ESTUDIO EPIDEMIOLÓGICO Y ABORDAJE INTEGRAL DE LA ENFERMEDAD DE HAJDU-CHENEY.

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Esto no hubiese sido posible sin ustedes, sinceramente, gracias.

A Noah.

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RESUMEN

Las enfermedades raras son aquellas cuya prevalencia es menor de 1 de cada 2.000 nacimientos vivos. Este tipo de patologías presentan una serie de características comunes como la cronicidad, el carácter degenerativo, su alto potencial discapacitante y las elevadas tasas de mortalidad. Además, en la mayoría de estas enfermedades existe un retraso en el diagnóstico definitivo y no suelen contar con un tratamiento específico y curativo. En concreto, el síndrome de Hajdu-Cheney (HCS), es una enfermedad rara de origen genético que pertenece al grupo de los síndromes acroosteolíticos, afectando principalmente al tejido conectivo. El síndrome es provocado por una mutación heterocigótica en el gen NOTCH2, concretamente en el cromosoma 1p13-p11, respondiendo a un patrón hereditario autosómico dominante, aunque se observan casos de carácter esporádico. La prevalencia de esta enfermedad es de menos de una persona entre un millón (<1/1000000).

Desde la primera descripción del síndrome realizada por N. Hajdu en 1948, se han descrito alrededor de 100 casos en la literatura científica observándose una serie de características generales comunes en todos ellos; la variabilidad fenotípica, el carácter degenerativo y un cuadro de osteolísis de las falanges distales y osteoporosis generalizada acompañado de otras manifestaciones clínicas.

El diagnóstico definitivo debe ser realizado mediante un estudio genético, aunque la orientación de este se realiza mediante la observación de la apariencia externa y los hallazgos radiológicos encontrados.

Existen nexos clínicos con otro tipo de enfermedades, como con la Esclerodermia, la Sarcoidosis, Progeria, Picnodisostosis, Whyte-Hemingway, Winchester y Síndrome de Alaguille con los que, en ocasiones, se aborda un diagnóstico diferencial.

Actualmente no existe un tratamiento farmacólogico eficaz y definitivo para este síndrome, aunque existen proyectos que estudian sobre este aspecto. El tratamiento actual para esta enfermedad está destinado al abordaje de las complicaciones y los problemas subyacentes ofreciendo una mejoría en la calidad y esperanza de vida.

Este proyecto pretende seguir las líneas de acción establecidas y recomendadas por IRDiRC, EUCERD y el Plan de Atención a personas afectadas por Enfermedades Raras elaborado por la Consejería de Salud de la Junta de Andalucía.

Marcándose como objetivo principal, avanzar en el conocimiento de la epidemiología del Síndrome Hajdu-Cheney, al objeto de planificar un mejor abordaje de este.

Para alcanzar ese propósito se realiza un estudio sobre los aspectos generales de las enfermedades raras con el fin de contextualizar el propio síndrome elegido, se realiza una actualización del conocimiento existente sobre la enfermedad, se describen dos casos diagnosticados en España y se elabora un plan de cuidados estándar de enfermería específico para el Síndrome de Hajdu-Cheney.

Este trabajo contribuye notablemente al desarrollo de esta enfermedad puesto que varios de los principales obstáculos que presentaban las investigaciones previas, como la escasez de conocimiento actualizado, la necesidad de describir nuevos casos diagnosticados para completar el fenotipo y establecer una planificación para mejorar el abordaje de la enfermedad, se tratan en esta tesis doctoral.

INTRODUCCIÓN GENERAL

El síndrome de Hajdu-Cheney está catalogado como una enfermedad rara del tejido conectivo, perteneciente al grupo de los síndromes acroosteolíticos. Para conocer los aspectos específicos sobre esta enfermedad, estudiar su abordaje clínico y su epidemiología se hace imprescindible entender previamente el panorama en el que se desarrollan este tipo de patologías poco frecuentes.

Las enfermedades raras son un tema de gran interés científico-sanitario que se encuentra en auge en los últimos años, siendo el abordaje y la atención integral una de las principales preocupaciones. Las enfermedades raras se definen como un conjunto de patologías cuyo principal rasgo es su baja prevalencia en la población [1]. También se las conoce como enfermedades minoritarias o poco frecuentes. Para ser considerada como rara, debe afectar a menos de 1 de cada 2.000 nacimientos vivos [2]. Existen entre 7.000 y 8.000 enfermedades raras actualmente. El 80% de este tipo de patologías tienen una etiología de carácter genético presentando heterogeneidad clínica y fenotípica debido a la variabilidad de expresión del gen mutado que las ocasiona. Una amplia mayoría del 20% restante, cuenta con un origen de carácter metabólico [3].

Para obtener una visión completa de la atención integral que precisa el campo de las enfermedades raras, y así profundizar en su abordaje, es necesario estudiar con precisión los diferentes aspectos de carácter clínico que circundan este tipo de patologías, las circunstancias específicas que cada enfermedad origina y las repercusiones entre la familia, el entorno y el propio paciente así como las relaciones existentes entre los anteriores estamentos [4].

Los principales problemas a los que se enfrentan los pacientes a los que se les diagnostica una de estas enfermedades son la cronicidad, su carácter degenerativo, su alto potencial discapacitante y las elevadas tasas de mortalidad [1]. Por tanto, este tipo de pacientes precisaran de intervenciones y cuidados de carácter holista y multidisciplinar.

Debido a la escasez de casos existentes de cada enfermedad y a la especificidad de estos, a veces, el conocimiento científico, y como consecuencia, la producción literaria al respecto es directamente proporcional al número de casos descritos [5]. Lo que indudablemente dificulta la obtención de conocimiento actualizado de este tipo de enfermedades. Otro aspecto fundamental, consecuencia de la baja prevalencia, y que obstaculiza la producción de conocimiento sobre estas patologías es la dispersión geográfica de los casos diagnosticados. Esta dispersión complica la formación de muestras lo suficientemente amplias como para realizar estudios de gran envergadura. Actualmente, sólo se ha generado conocimiento científico, aproximadamente, para 800 de estas enfermedades [3].

Este hecho repercute negativamente a la fase diagnóstica donde se concibe complejo realizar un diagnóstico precoz y certero. El retraso en el diagnóstico [6] obstaculiza el abordaje clínico de la enfermedad sumergiendo al paciente en una situación de incertidumbre y caos que influye nocivamente en su estado de salud, agravando los síntomas de la enfermedad y potenciando la aparición de trastornos

mentales. El retraso en el diagnóstico supone un gran problema para este campo, un paciente puede tardar de media entre 4-5 años para obtener un diagnóstico. El 20% de los pacientes tardan aproximadamente 10 años en obtenerlo [3]. En la mayoría de los casos, existe un retraso en el diagnóstico debido al desconocimiento generalizado en el campo de las enfermedades raras, las dificultades para acceder a la información necesaria, un número insuficiente de profesionales y centros sanitarios especializados, además de la baja prevalencia y los nexos clínicos existentes entre estas patologías.

La depresión y la ansiedad son los trastornos más comunes en las enfermedades de larga duración [7,8]. La mayoría de los pacientes diagnosticados o en fase de diagnóstico de una enfermedad rara sufre de ansiedad y depresión por la incertidumbre en cuanto a su situación de salud, aumentando la carga psicológica y su psicopatología [9,10]. Es preciso destacar los acontecimientos vividos recientemente con la época de pandemia por Covid19, ya que influyeron negativamente sobre la atención sanitaria a este tipo de pacientes y en especial a su estado de salud mental.

El 30 de Enero de 2020 la Organización Mundial de la salud declaró que el brote de Covid19 era una emergencia sanitaria a nivel mundial [11]. Desde entonces muchos gobiernos impusieron medidas que obligaban al aislamiento y al distanciamiento social. Concretamente en España [12] se implantaron unas medidas de confinamiento domiciliario quedando totalmente prohibido el funcionamiento de los servicios no esenciales y la deambulación libre y ociosa no justificada. Los centros educativos permanecieron cerrados y el uso de mascarilla fue obligatorio, al igual que el distanciamiento social de 2 metros. Estas medidas se mantuvieron desde el 14 de Marzo hasta finales de Junio. Con el paso del tiempo se observaba como los gobiernos aplicaban o retiraban medidas dependiendo del estado de la pandemia por Covid19 en el país. Estas medidas han restringido el acceso a la atención médica primaria, los servicios de salud mental y otro tipo de centros de apoyo que se han visto gravemente interrumpidos.

Esta pandemia y las medidas de salud pública implementadas produjeron graves repercusiones psicológicas en cualquier persona.

Atendiendo a lo descrito anteriormente, los pacientes que padecen una enfermedad rara presentaron un riesgo particular de sufrir alteraciones psicológicas debilitantes como consecuencia de esta pandemia siendo un grupo de población vulnerable.

La búsqueda de tratamientos eficaces y curativos ocupa el mayor interés científico en este campo. A pesar de que los avances de la comunidad científica sobre estas enfermedades son indudables, hasta la fecha el 42,68% de las personas con estas patologías no dispone de tratamiento o si lo dispone, no es el adecuado [3]. El abordaje de estas patologías se basa en el tratamiento de las diferentes complicaciones clínicas y en la valoración de las necesidades de cada individuo para proporcionar unos cuidados que aumenten la calidad de vida.

La investigación en este campo progresa favorablemente en los últimos años, a pesar de los obstáculos que presenta el estudio de estos tipos de patologías.

Para proporcionar una atención sanitaria de calidad es imprescindible que los profesionales que prestan la atención cuenten con; conocimientos y experiencia en la asistencia a estas patologías, recursos necesarios y se establezca una adecuada coordinación entre los distintos profesionales implicados en la atención. Para ello, es esencial la actualización de la información disponible; el registro y descripción de casos, la planificación de guías y protocolos específicos que mejoren la práctica clínica. El enfoque multidisciplinar que necesita el mundo de las enfermedades raras debe tener en cuenta la perspectiva de todos los ámbitos de la sanidad [9].

La planificación de la atención a las personas afectadas por una enfermedad rara debe plantearse desde una perspectiva multidisciplinar y colaborativa que incluya los aspectos sanitarios, sociales y psicológicos de cada paciente [1].

En la atención a las enfermedades raras tienen un papel fundamental las Unidades de Referencia con experiencia en la Atención a las Enfermedades Raras y los Centros, Servicios y Unidades de Referencia del Sistema del Sistema Nacional de Salud (CSUR)[13].

Actualmente, en Andalucía existen 39 CSUR designados, además de Unidades de Referencia Autonómica para ELA, fibrosis quística, porfirias, extrofia vesical y epispadias y disfonía espasmódica [14]. Diez de estos CSUR pertenecen a ERNs (European Reference Networks) [15].

La clave del abordaje y la atención integral empieza por situar al paciente en el centro de la estructura, garantizando una atención multidisciplinar y colaborativa de todos los profesionales sanitarios. La participación en la toma de decisiones por parte del paciente es crucial y necesaria en estos casos, siendo la familia y el entorno componentes básicos en el tratamiento de este aspecto.

Cabe destacar el rol de las asociaciones de pacientes en el campo de las enfermedades raras. Este tipo de asociaciones conforman un sólido entramado que sirve de soporte en diferentes aspectos para este tipo de pacientes. Ofrecen información actualizada sobre las enfermedades, realizan una acogida al paciente recién diagnosticado y establecen contactos entre pacientes que padecen el mismo tipo de enfermedad. Al mismo tiempo conforman un importante movimiento caracterizado por su entrega desinteresada en el avance de este tipo de patologías.

Atendiendo al marco teórico en que se desarrollan las enfermedades raras y a las generalidades anteriormente comentadas, el estudio de cualquier enfermedad específica será más accesible. En concreto, en el caso del Síndrome de Hajdu-Cheney se observará que presenta la mayoría de los aspectos descritos.

El Síndrome de Hajdu-Cheney (HCS) es una enfermedad rara de origen genético. Responde a las referencias #102500 en la base de datos de OMIM y ORPHA955 en ORPHANET. Es una patología perteneciente al grupo de los síndromes acroosteolíticos [16] que afecta principalmente al tejido conectivo. Acro-dento-osteo-displasia, acroosteolísis con osteoporosis y cambios en el cráneo y la mandíbula, artodentroosteodisplasia y síndrome del peroné serpentino y riñones poliquísticos son

otras nomenclaturas a las que responde. El síndrome es provocado por una mutación heterocigótica en el gen NOTCH2 [17] concretamente en el cromosoma 1p13-p11, respondiendo a un patrón hereditario autosómico dominante [18], aunque se observan casos de carácter esporádico [19]. La prevalencia de esta enfermedad es de menos de una persona entre un millón (<1/1000000).

Hajdu y Kauntze realizaron la primera descripción de la enfermedad en 1948 [20] , más tarde en 1965 esta descripción fue completada por D. Cheney [21]. Desde entonces se han descrito alrededor de 100 casos en la literatura científica observándose una serie de características generales comunes en todos ellos; la variabilidad fenotípica, el carácter degenerativo y un cuadro de osteolísis de las falanges distales y osteoporosis generalizada acompañado de otras manifestaciones clínicas.

La variabilidad fenotípica [22] es consecuencia de la propia variabilidad de expresión de NOTCH2 pudiéndose encontrar pacientes diagnosticados de este síndrome con diferencias clínicas entre sí. Además, el espectro clínico de esta patología es muy amplio y difícilmente observable por completo en un solo caso.

La enfermedad cuenta con un carácter degenerativo [23] por lo que las manifestaciones clínicas se agravan con el paso del tiempo, presentando cambios desde la primera infancia hasta la adultez tardía.

El cuadro de osteólisis de las falanges distales y osteoporosis generalizada [24] que se observa en todos los casos, se acompaña de una serie de manifestaciones clínicas que como se ha expuesto anteriormente, pueden ser diferentes entre pacientes.

Estas diferencias comprenden alteraciones craneales [20]; como dolicocefalia, cierre tardío de suturas craneales, presencia de múltiples huesos wormianos, ausencia de senos frontales, cresta occipital prominente, batrocefalia, silla turca alargada y micrognatia, entre otras, siendo posibles complicaciones la invaginación basilar [25], la hidrocefalia [26] y siringomelia [27]. Alteraciones faciales; como hipertelorismo, sinofridia, cabello grueso, orejas de implantación baja, filtrum largo, mandíbula pequeña, paladar arqueado, pérdida prematura de dientes [28], voz anormalmente profunda e hirsutismo, entre otras. Alteraciones a nivel del musculoesquelético; como cifosis, escoliosis, talla baja [29], fracturas de huesos largos, acroosteolísis [30], resorción ósea distal progresiva, laxitud articular, desmineralización esquelética y osteoporosis [31]. Problemas auditivos y del habla y alteraciones en el desarrollo motor. Cardiopatías congénitas [32], así como malformaciones en los aparatos respiratorio, renal [33] y digestivo. Úlceras plantares y hernias. Cabe destacar la existencia de un subgrupo de pacientes dentro de este síndrome que presentan peroné serpentino y riñones poliquísticos [34,35].

El diagnóstico definitivo debe ser realizado mediante un estudio genético [36], aunque la orientación del mismo se realiza mediante la observación de la apariencia externa y los hallazgos radiológicos encontrados [37]. Existen nexos clínicos con otro tipo de enfermedades [38] como con la Esclerodermia, la Sarcoidosis, Progeria,

Picnodisostosis, Whyte-Hemingway, Winchester y Síndrome de Alaguille con los que, en ocasiones, se aborda un diagnóstico diferencial.

Actualmente no existe un tratamiento farmacólogico eficaz y definitivo para este síndrome, aunque existen proyectos que estudian sobre este aspecto [39]. El tratamiento actual para esta enfermedad está destinado al abordaje de las complicaciones y los problemas subyacentes ofreciendo una mejoría en la calidad y esperanza de vida.

Justificación

En general las enfermedades raras y en particular el Síndrome de Hajdu-Cheney cuentan con una escasa prevalencia y pocos casos registrados. Nos encontramos ante una muestra poblacional de estudio dispersa, con un fenotipo variable y una clínica poco descrita y de diferente evolución.

Atendiendo a las características básicas de este tipo de patologías y en concreto a este síndrome, nos encontramos con un campo de estudio con muchas vertientes por explorar, destacando aspectos como el estudio de las generalidades del mundo de las enfermedades raras, la definición completa del fenotipo y la clínica, la actualización de los casos descritos, el registro en fuentes oficiales y la elaboración de un protocolo de actuación específico para esta patología ya que todos estos aspectos facilitarían el abordaje de este síndrome y consiguientemente podría mejorar la calidad y esperanza de vida de los pacientes.

A pesar de que los avances de la comunidad científica sobre esta enfermedad son indudables y ya se conoce el origen genético y se entienden los procesos en los que se desarrolla la enfermedad, hasta la fecha el abordaje se basa en el tratamiento de las diferentes complicaciones clínicas y en la valoración de las necesidades de cada individuo para proporcionar unos cuidados que aumenten la calidad de vida.

Debido a la baja prevalencia y a la escasez de casos documentados, obtener una descripción completa y con perspectiva de la enfermedad se hace ciertamente difícil. La dispersión geográfica de los casos descritos, el espacio de tiempo entre ellos, la carencia de seguimiento evaluativo constante de los pacientes informados y la ausencia de protocolos descriptivos específicos para esta enfermedad obstaculizan el desarrollo y la investigación de esta patología.

Centrándonos en la multitud de manifestaciones clínicas, con las que cuenta el síndrome de Hajdu-Cheney que muestran fenotipos con algunas diferencias entre ellos y que estos signos evolucionan con el tiempo, sumado al amplio abanico de enfermedades con las que existen nexos clínicos y pueden surgir dudas diagnósticas, realizar un diagnóstico precoz y definitivo se presenta complejo.

Observando el panorama científico-clínico donde se desarrolla esta patología cabe destacar que la estandarización y universalización en la valoración y la realización de pruebas diagnósticas facilitarían el flujo y el progreso en el mundo de la investigación.

Una descripción de casos detallada mejoraría los tiempos de diagnóstico, elevando la calidad en el tratamiento y ofreciendo una mejor asistencia global a cada paciente.

La actualización de casos descritos de pacientes con HCS sería de gran interés para realizar un estudio transversal y con perspectiva, obteniendo de esta manera una visión global y conjunta de la patología.

Por lo que examinar con exactitud las diferencias entre fenotipos, definir una clínica y una evolución especifica de la enfermedad y realizar un plan de intervención específico para los pacientes con esta enfermedad, haría que el abordaje de la enfermedad fuera más eficaz.

El conocimiento actualizado sobre este campo repercutirá en la mejora de la calidad asistencial sanitaria y en la calidad de vida de pacientes y familias que sufren enfermedades raras.

Todas estas líneas de acción siguen las líneas de trabajo establecidas y recomendadas por IRDiRC, EUCERD y el Plan de Atención a personas afectadas por Enfermedades Raras elaborado por la Consejería de Salud de la Junta de Andalucía.

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OBJETIVOS

Objetivo principal:

Avanzar en el conocimiento de la epidemiología del Síndrome Hajdu-Cheney, al objeto de planificar un mejor abordaje del mismo.

Objetivos específicos:

- Estudiar los aspectos generales de las enfermedades raras.

- Realizar una revisión sistemática de la literatura sobre el Síndrome de Hajdu-Cheney para obtener la información necesaria y establecer el punto de partida del estudio.

- Descripción de nuevos casos diagnosticados del Síndrome de Hajdu-Cheney.

- Realizar un plan de cuidados estándar de enfermería específico para el Síndrome de Hajdu-Cheney.

METODOLOGÍA

Diseño

Se ha diseñado un estudio observacional transversal.

Ámbito y periodo del estudio

El estudio se realizó a nivel internacional, para ello se procedió a contactar con los diferentes autores y entidades que han descrito casos del Síndrome de Hajdu-Cheney, a la vez que con asociaciones de enfermedades raras que reportaron pacientes con este diagnóstico.

Este proyecto forma parte del Programa de Doctorado de Medicina Clínica y Salud Pública de la Universidad de Granada.

Fases

- **Fase 0:** Diseño y planificación.

En esta primera fase se diseñó el estudio, se realizó la planificación del trabajo y el plan de investigación.

El estudio fue aprobado por el Comité de Ética de la Investigación de la ciudad de Granada (CEI-Granada) con fecha 02/03/2021.

- **Fase 1:** Contextualización del campo de estudio.

En esta fase se estudiaron los aspectos generales del mundo de las enfermedades raras con el objetivo de llegar a un mejor entendimiento del propio Síndrome de Hajdu-Cheney. Al analizar el escenario en el que se desarrolla este tipo de patologías se obtuvieron las claves para fundamentar y gestionar los resultados de esta tesis. Para lograr este objetivo se estudiaron otras enfermedades raras desde diferentes perspectivas, prestando mayor atención a las necesidades que este campo de estudio precisa.

- **Fase 2:** Estado del arte.

Se realizó una revisión sistemática de la literatura científica publicada sobre el síndrome de Hajdu-Cheney.

La búsqueda de la bibliografía se efectuó en las principales bases de datos de enfermedades raras, tales como Orphanet, y otras bases de datos como Pubmed, Scielo, entre otras.

El lenguaje estructurado empleado se obtuvo mediante los términos MeSH y los descriptores de Ciencias de la salud (DeCS). Los descriptores fueron “Hajdu-Cheney Syndrome”, “Acro-Osteolysis”, “Receptor, Notch2”,

"Connective tissue" y "Rare diseases", y los operadores booleanos empleados fueron AND y OR.

La revisión sistemática se llevó a cabo siguiendo un protocolo, disponible en la web: http://www.crd.york.ac.uk/PROSPERO/ y cuyo número de registro es CRD42020164377.

Todo ello siguiendo el protocolo de revisión Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Los resultados de nuestra revisión han servido en esta tesis para reunir la información descrita en la literatura referente a dicha enfermedad.

- **Fase 3:** Contacto con las diferentes entidades relacionadas con HCS.

Una vez obtenidos los resultados de nuestra revisión, se estableció contacto con las diferentes entidades, ya localizadas, que han descrito casos de la enfermedad (hospitales, universidades, asociaciones, centros de investigación, etc.). Además, se procedió a contactar con cada uno de los autores de referencia de los artículos usados en la revisión sistemática, con el fin de visibilizar los datos recopilados y establecer un feed-back colaborativo que repercutió positivamente en el estudio. Se intentó reunir el máximo número de casos para la conformación de una muestra poblacional específica para futuras líneas de investigación sobre el tema.

- **Fase 4:** Descripción de nuevos casos.

Con la información obtenida hasta el momento se definió de forma exhaustiva el fenotipo y la clínica de esta enfermedad. Para ello se realizaron descripciones de nuevos casos y se analizaron de forma conjunta con el resto de los casos publicados.

- **Fase 5:** Elaboración del Plan de Cuidados.

Tras el estudio de los resultados obtenidos, se realizó un plan de cuidados de enfermería usando taxonomía NANDA-NIC-NOC. Esta fase nos ha posibilitado elaborar un plan para valorar las necesidades específicas para HCS, marcando una serie de objetivos a alcanzar mediante una serie de intervenciones de enfermería. Actualmente, no existe un tratamiento eficaz para esta patología, por lo tanto, el abordaje de HCS se centra en ofrecer una mayor calidad de vida a los pacientes que la padecen lo que justifica la necesidad de un plan de cuidados específico para esta enfermedad.

- **Fase 6:** Publicación.

Una vez obtenidos los resultados, se difundieron los mismos a través de revistas científicas y congresos nacionales e internacionales que estudian enfermedades minoritarias.

ASPECTOS ÉTICOS

Principios generales

Este plan de investigación clínica se ha preparado con pleno entendimiento y de acuerdo con las normas de Buena Práctica Clínica de conformidad con CPMP/ICH/135/95, con la Declaración de Helsinki, la ISO 14155 y todas las directrices nacionales relevantes. En las normas mencionadas se establecen claramente las responsabilidades de cada uno de los investigadores.

Declaración de Helsinki

El investigador principal del estudio garantizará que el estudio se realiza conforme a los principios de la Declaración de Helsinki (64ª Asamblea General, Fortaleza, Brasil, octubre 2013).

Comité ético de investigación clínica

La aprobación por el Comité Ético de Investigación Clínica era condición indispensable para la realización del estudio. La aprobación de dicho plan de investigación se obtuvo antes de la inclusión de los voluntarios en la investigación. El estudio se presentó al Comité Ético de Investigación Provincial de Granada (CEI-Granada).

Consentimiento informado del voluntario

El investigador es responsable de obtener y documentar el consentimiento informado escrito, libremente expresado, de todos los voluntarios antes de su participación en el estudio (Real Decreto 223/2004).

Los voluntarios fueron informados de los objetivos, métodos, beneficios previstos y riesgos potenciales del estudio clínico. Recibió una copia del consentimiento informado firmada.

Información confidencial

Todos los datos carácter personal, obtenidos en este estudio son confidenciales y se trataron conforme a la Ley Orgánica de Protección de Datos de Carácter Personal 15/99.

Para garantizar la confidencialidad toda la información personal generada en este estudio fue considerada altamente confidencial y no se divulgó ni se divulgará a ninguna persona no implicada directamente en el estudio. La información obtenida se utilizará exclusivamente para los fines específicos de este estudio. En las publicaciones científicas que se generen en ningún caso figurarán datos personales que pudieran identificar a los voluntarios.

RESULTADOS

CAPÍTULO 1

Con objeto de conseguir el primer objetivo específico se procedió a estudiar los aspectos generales de las enfermedades raras. Hecho que fue aprovechado durante el confinamiento ocurrido en la pandemia causada por el COVID-19.

Posteriormente se redactó un artículo con los datos recogidos que fue publicado con el título:

Depression and anxiety in patients with rare diseases during the Covid-19 pandemic.

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Depression and Anxiety in Patients with Rare Diseases during the COVID-19 Pandemic

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Abstract: Scientific knowledge on depression and anxiety in patients with rare diseases during the COVID-19 pandemic is scarce; however, it is essential to perform comprehensive management of these patients. The aim of this study was to research how the situation caused by the SARS-CoV-2 pandemic has influenced the lives of patients with rare diseases regarding depression and anxiety. This Spanish study considered a heterogeneous population sample of 86 patients with confirmed diagnosis of different rare diseases. Participants took part in a cross-sectional online study by completing specific questionnaires on the study topic. Depression was measured using the Patient Health Questionnaire (PHQ-9), and the General Anxiety Disorder Scale (GAD-7) was used for evaluating anxiety. Data collection through an online questionnaire allowed for a greater population scope and therefore the inclusion patients of other nationalities in the study sample. Finally, as a general result, this study found that, in the face of the pandemic, anxiety and depression remained at a higher level in this group than in the general population, making these patients a vulnerable population group.

Keywords: rare disease; depression; anxiety; COVID-19; SARS CoV-2; pandemic

1. Introduction

Rare diseases are conditions that are mainly characterized by their low prevalence in the population [1]. They are also known as orphan diseases. In order to be considered a rare disease, it must affect fewer than 1 in 2000 people [2]. There may be as many as 7000 rare diseases, 80% of which are genetic. These diseases are clinically and phenotypically very heterogeneous due to the variability of expression of the mutated gene that causes them. Most of these diseases are chronic and progressive and normally have an important negative impact on the quality of life of the affected patients [1].

In order to fully grasp the complexity of rare diseases, it is necessary to study in depth the different clinical aspects that characterize them, the specific circumstances that surround each disease, and the repercussions they have on patients, their families and their environment, as well as the interactions between the previously mentioned elements [3].

Due to the low number of cases and the specificity of each disease, it is often the case that scientific knowledge, and therefore, the scientific literature on each disease is directly proportional to the number of cases that have been described [4].

This fact has a negative impact on the diagnostic phase, making it hard to establish a definitive diagnosis at early stages. Diagnostic delay [5] hinders clinical management of the disease, leading to a situation of uncertainty and chaos that is harmful for the patient, worsening the symptoms of their disease and increasing the likelihood of development of mental disorders.

On 11 March 2020, the World Health Organization declared the infectious disease caused by the coronavirus discovered in 2019, named COVID-19, a pandemic [6]. Since then, many governments have imposed a series of measures that make isolation and social distancing compulsory. Namely, in Spain [7], the country in which this study was carried out, measures of home confinement were established, and all non-essential services were prohibited, as was free, non-justified circulation. Schools were closed and the use of face masks was made obligatory, as was a social distance of 2 m. These measures remained in place from 14 March to the end of June 2020. Over time, we have seen how the government applied or lifted impositions depending on the state of the COVID-19 pandemic throughout the country. These measures have limited the access to primary medical care, and access to mental health services and other types of support centers has been greatly disrupted.

This pandemic and the public health measures that were established can have serious psychological repercussions on any person. Additionally, patients with rare diseases may be at risk of suffering debilitating psychological symptoms as a direct consequence of the progression of their own disease [3]. Additionally, the development of this pandemic negatively impacts these patients, who have become a vulnerable population group with regard to the issue at hand [8].

There are studies that report the psychological burden and the increase in mental health symptoms in patients with rare diseases [8,9]. The increase in depressive and anxiety syndromes in certain rare diseases is also known [10], but in general, scientific publications on the psychopathology of rare diseases are scarce and, even more so, with regard to how they may relate to the worldwide COVID-19 pandemic.

Depression and anxiety are frequent psychosocial symptoms in chronic diseases [11]. Depression is a frequent mental disorder that is characterized by persistent sadness and a loss of interest in activities that are normally enjoyable, accompanied by an incapability to carry out daily activities. Anxiety is an emotional response that arises in the face of situations that the person perceives or interprets as menacing or dangerous [12].

As no curative treatment exists for most rare diseases [1], it is of interest to study depression and anxiety as related symptoms in a specific context, such as that generated by the COVID-19 pandemic, as the treatment of such symptoms would likely improve the global quality of life of these patients.

The aim of this study was to research how the situation caused by the SARS-CoV-2 pandemic has influenced the lives of patients with rare diseases regarding depression and anxiety.

2. Materials and Methods

This study was a cross-sectional online study. Due to the pandemic situation caused by the coronavirus SARS-CoV-2, the whole study was carried out using online questionnaires. This way, it was possible for the study to acquire an international perspective.

The study was approved by the Ethics Committee of the province of Granada. At all times, the study was performed in accordance with the guidelines of the Helsinki Declaration, amended by the 64th General Assembly of the AMM, in Fortaleza, Brazil, in October 2013. Before completing the online questionnaire, participants were requested to give their informed consent online, by means of a box on the form that had to be intentionally ticked in order to continue with the questionnaire.

2.1. Participants

Patients were recruited through rare disease patient associations. Information on the study was distributed via mailing lists of rare disease patient associations. An information leaflet with information on the study was attached and the email included a link to an online form specifically designed for this study (see in Supplementary Materials).

A special email address was created for this study, through which patients interested in taking part could contact the research team with any questions.

All patients diagnosed with a rare disease could take part in the study. Diseases with a prevalence of 1 in 2000 people were considered rare diseases and included in the study. If no information regarding prevalence was available, patients were included if their disease is listed on the Orpha.net registry of rare diseases [2].

The minimum age for participation in the study was 18 years of age, with no upper limit. Patients with an unclear diagnosis, with a disease not considered a rare disease, or patients who said that the diagnosis was not given by a doctor were excluded.

The patients who answered "Yes" to the question "Do you have a recent history of symptoms of anxiety or depression in the months prior to the pandemic?" were excluded. Extensive lists of symptoms of anxiety and depression were detailed in the question. The symptoms of anxiety considered include psychological symptoms such as constant worry, tiredness, irritability, and difficulty concentrating or sleeping problems, and physical symptoms such as high heart rate, excessive sweating, muscle tension, shaking, dizziness, and fainting. The symptoms of depression considered include irritable mood or an overall low mood, sleep disorders (difficulty getting to sleep or excessive sleeping), changes in appetite (often with associated weight changes), tiredness and low energy, feelings of uselessness, self-hate and guilt, difficulty concentrating, slow or fast movements, feelings of hopelessness or abandonment, repetitive thoughts regarding death or suicidal thinking, and loss of pleasure in things that normally bring joy, including sexual activity.

The main researcher evaluated each questionnaire and those which did not fulfill the three requirements (>18 years of age, confirmed diagnosis of a rare disease, and no recent history of anxiety or depression) were excluded from the study.

Patients who failed to complete more than 85% of the questionnaire were also excluded.

2.2. Instruments

Depression was measured by the Patient Health Questionnaire (PHQ-9), an instrument that scores 9 items that determine the level of severity of depressive symptoms [13–15].

Cut-off points of a total score of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively. A score of 10 or above is recommended by the authors as a single cut-off point for major depression. The instrument has an excellent internal reliability ($\alpha = 0.89$), excellent test–retest reliability, and criterion and construct validity [13].

Anxiety was evaluated by the General Anxiety Disorder scale (GAD-7) [15–17]. It consists of seven questions that can be scored between 0 and 3; therefore, the minimum and maximum scores possible are 0 and 21, respectively. To evaluate the results obtained from the answered questionnaires, its authors suggest the following scores: 0–4, no anxiety detected, 5–9, symptoms of mild anxiety detected, 10–14, symptoms of moderate anxiety detected, and 15–21, symptoms of severe anxiety detected. It is recommended that consultation with a healthcare professional should be sought if a score of 10 or above is obtained.

Although it has the best operational characteristics for the detection of general anxiety disorder, the instrument has proven to be useful in the detection of any other anxiety disorder. The GAD–7 scale presents an excellent internal reliability ($\alpha = 0.92$), good test–retest reliability ($ICC = 0.83$) as well as criterion, construct, factorial, and procedural validity.

2.3. Statistical Analyzsis

Mean and standard deviation were calculated for quantitative variables. Qualitative variables were reported using frequencies.

The Kolmogorov–Smirnov test was applied to test for normal distribution of the variables PHQ-9 score and GAD-7 score; of the two, the PHQ-9 could be considered normal ($p = 0.11$), a skewness of 0.96 and a kurtosis of 0.33.

Student's t–test was used to determine if there were differences between PHQ-9 and GAD-7 scores according to whether the participant had been ill with COVID-19, had been in close contact with a COVID-19 patient, had non-cohabiting family members or friends who had been ill with COVID-19, had family members or close friends pass away due to COVID-19, age, gender, education level, marital status, and body mass index.

The relationship between quantitative and categorical variables was measured using the chi square test.

The relation between depression and anxiety was calculated applying Pearson's correlation coefficient.

3. Results

To assess the reliability of the questionnaires, Cronbach's alpha coefficient was calculated. For the questionnaire that measures depression, the Patient Health Questionnaire (PHQ-9), the Cronbach's alpha coefficient was 0.90, whereas for the questionnaire that measures anxiety, the General Anxiety Disorder scale (GAD-7), the coefficient was 0.94. Overall, when all items were considered, the result was 0.95.

We analyzed a sample of 86 individuals, 76% of whom were female, and the mean age of the study group was 42.74 years ($SD = 13.43$). The majority of those surveyed, 95% (82 patients), lived in Spain, but there were also participants from Chile, Colombia, Holland and Mexico. Nearly one third of the participants (33%) were not in paid employment, either due to retirement or to recognition of permanent disability.

More than half of the participants, 57%, were married, followed by 33% who were single. Most of the participants in the study (54%) had university level education, an additional 9% had upper level professional training, and 14% had baccalaureate or middle level training.

At the time of reporting, 89% did not use tobacco and only 13% drank alcohol regularly.

Six participants (7%) had been ill with COVID-19, all of whom were symptomatic, and none required hospital admission. Regarding the symptoms experienced by the participants who had COVID-19, the highest percentages were found for dry cough and tiredness, followed by muscular pain and fever.

A minimum ten-day quarantine had to be completed by 21% (18 cases) of participants due to having close contact with someone who had COVID-19, and 45% (39 cases) had family members or close friends who had COVID-19 but did not have to be quarantined. We found that 14% (12 cases) had lost at least one family member or close friend due to COVID-19.

Analyzing the responses to the GAD-7 questionnaire, we observed no statistically significant differences between sexes $\chi^2(3, N = 86) = 0.21$, $p = 0.98$, and found that 74% did not have symptoms of anxiety or had mild symptoms (Table 1). Examining the answers according to education level, we found that among those with severe anxiety, there was a majority of individuals with university degrees (70%).

Table 1. General Anxiety Disorder scale (GAD-7) questionnaire scores according to sex of the studied population.

		No	Mild	Moderate	Severe	Total
Women	*n*	20	28	9	8	65
	% within sex	31	43	14	12	100
	% within GAD-7	77	74	75	80	76
Men	*n*	6	10	3	2	21
	% within sex	29	48	14	9	100
	% within GAD-7	23	26	25	20	24
Total	*n*	26	38	12	10	86
	% within sex	30	44	14	12	100
	% within GAD-7	100	100	100	100	100

Regarding level of depression according to the score obtained from the PHQ-9 questionnaire, we found that 70% of the participants did not have symptoms of depression, or such symptoms were mild or very mild. Only 16% (14 individuals) had moderately severe or severe symptoms. The PHQ-9 scores were not associated to sex $\chi^2(4, n = 86) = 2.24$, $p = 0.69$ (Table 2).

Table 2. Patient Health Questionnaire (PHQ-9) scores according to sex of the studied population.

		No	Mild	Moderate	Moderately Severe	Severe	Total
Women	*n*	22	21	10	7	5	65
	% within sex	34	32	15	11	8	100
	% within GAD-7	76	68	83	87	83	76
Men	*n*	7	10	2	1	1	21
	% within sex	33	48	9	5	5	100
	% within GAD-7	24	32	17	12	17	24
Total	*n*	29	31	12	8	6	86
	% within sex	34	36	14	9	7	100
	% within GAD-7	100	100	100	100	100	100

We found no statistically significant differences according to body mass index, nor according to age in GAD-7 and PHQ-9 questionnaire scores.

There was a strong correlation $r(86) = 0.75$, $p < 0.001$, between the GAD-7 and PHQ-9 questionnaire scores, indicating that those who had the highest levels of anxiety were also likely to have high levels of depression.

Table 3 shows the mean and standard deviations according to the answers to the questions regarding COVID-19. Additionally, we used the *t* test to calculate the *p* value for the comparison of the groups formed according to answer.

Table 3. Comparison of means and standard deviation according to answers by PHQ-9 and GAD-7 scores.

		YES	NO	P
Have you been ill with COVID-19?	PHQ–9	7.50 (5.28)	7.81 (6.46)	0.91
	GAD–7	6.67 (3.39)	7.36 (5.57)	0.76
If you did not have COVID-19, have you been a close contact of a COVID-19 patient?	PHQ–9	6.83 (6.18)	8.04 (6.42)	0.48
	GAD–7	7.39 (5.49)	7.29 (5.46)	0.95
Have any of your non cohabiting family members or close friends been ill with COVID-19?	PHQ–9	9.49 (6.30)	6.38 (6.12)	0.02
	GAD–7	7.82 (5.66)	6.89 (5.26)	0.43
Have any of your family members or close friends passed away due to COVID-19?	PHQ–9	10.33 (7.30)	7.38 (6.14)	0.14
	GAD–7	9.58 (6.68)	6.95 (5.16)	0.12

As shown in Table 3, there were only differences in PHQ-9 scores amongst those who had family members or close friends who had been ill with COVID-19 and those

who did not. The highest score was found in those who had family members or friends who had COVID-19. We found no differences in scores regarding sex, marital status or education level.

4. Discussion

This research studied the impact on health and psychological wellbeing in patients with rare diseases during the COVID-19 pandemic. More specifically, it focused on the evaluation of the degree of anxiety and/or depression that patients with rare diseases may have experienced during the pandemic. Patients with rare diseases are patients with high requirements of healthcare; however, throughout the pandemic, access to healthcare services has been limited and, in many cases, non-existent [18].

We have not found specific studies evaluating depression and anxiety in patients with rare diseases during the pandemic. During our literature search, we only retrieved one study, published prior to the pandemic, that focused on the same area of research as the present study [19]. For this reason, we reviewed and used the literature on rare diseases in general and specific rare diseases, and on chronic and rare diseases in which depression and anxiety have been studied. We do not disregard the possibility of pursuing new future lines of research to study all kinds of factors that affect anxiety and depression as well as sexual disfunction in patients with rare diseases [15,20].

In order to evaluate the depression parameter, we used the validated PHQ-9 questionnaire, which has been proven to be precise in the evaluation of depressive states [21]. This questionnaire has been evaluated and has been proven to have good psychometric properties. Therefore, it is considered an exact diagnostic tool for depressive states [22], and it has been utilized by other authors to evaluate depression in patients with rare diseases [4]. The contrast of results with those obtained in similar circumstances using the same tools is therefore possible.

Our results indicate that 70% of the patients considered did not show signs of depression or had some form of mild depression. Meanwhile, only 30% reported levels of moderately severe depression. We also demonstrated that the highest percentages of moderate to severe depression are found in female patients (34% of patients within same sex) compared to male patients (20%). In the study on depression and anxiety in patients with rare diseases published in 2019 [19], the results show that 42% of patients had symptoms of moderate or severe depression compared to the 34% found in this study. However, in other studies that focused on depression and anxiety during the pandemic [23,24] in the general population, rates of depression were at 16% [24] and 19% [23], respectively. In a comparison of the prevalence of depression in the general population during the pandemic and the prevalence in patients with rare diseases, our study found that the prevalence of depression in patients with rare diseases was nearly double that of the general population (30%).

For the study and evaluation of anxiety, we used the validated GAD-7 questionnaire. This questionnaire has been used in previous studies with the same purpose [19,23]. The data obtained in our study indicated that 26% of the patients considered had severe anxiety compared to 74% who had mild anxiety or no symptoms of anxiety. In the previously mentioned study in patients with rare diseases published prior to the pandemic [19], researchers found that 23% of patients had anxiety. In studies carried out in the general population during the pandemic, the results show percentages of moderate to severe anxiety of 14% [22] and 29% [23], respectively.

In the systematic review carried out by Xiong et al. [25], where they analyzed 19 articles that considered anxiety and depression in the general population during the pandemic, rates of anxiety ranged from 6% to 19%. The results obtained in our study of patients with rare diseases were higher, with the prevalence of depression ranging between 15% and 48%. These results for depression do not constitute a significant difference between the general population group and the results of this study. In their study, Xiong et al. also demonstrated that women had a higher rate of symptoms of depression than men [25], as did other studies [23] on depression and anxiety in the general population. The age

group most affected was those younger than 40 years of age, and in our study, we found no relevance in the prevalence according to age.

On the other hand, there is a study on the impact of the pandemic in patients with rare diseases that demonstrates that 66% of the patients included in the study found their health care affected in some way during the pandemic. Around 46% of the study population suffered direct effects on their health status and wellbeing. Additionally, 79% reported that the pandemic had affected their mental health [25]. We did not find any articles including situational parameters regarding COVID-19 (Have you been ill with COVID-19? Have you been a close contact? etc.) such as those considered in this study in relation to anxiety and depression in patients with rare diseases.

In this study, we demonstrated that those patients who had family members or friends who were ill with COVID-19, even if they did not live together, had more symptoms of anxiety and depression than those who had been ill themselves or had been a close contact ($p = 0.02$). We did not find other published studies that relate depression and anxiety parameters with the patient's situation regarding COVID-19 in order to contrast this fact.

This study was performed using an online cross-sectional design, the method of preference for other similar studies [19,26,27]. Among the weaknesses of cross-sectional studies is the inability to determine the temporal relation between outcomes and risk factors, so they are unable to establish if the exposure preceded the disease or vice versa. Therefore, in our study, it is not possible to know if the symptoms of depression or anxiety were present prior to the pandemic or arose due such circumstances.

Our sample included 86 patients, which constitutes a high "n" for the type of patients considered. Other studies on patients with rare diseases have been performed in as few as 15 patients [26]. Recruitment of this sample was carried out online, using online forms for data collection, due to the state of emergency decreed by the national government. This method has been used by other authors, including Ozamiz-Etxebarria [28], to collect information during the pandemic period. The main advantages of this method, compared to previous research methods, include privacy and timely management and access to the results. This study included a patient support system for study participants, so patients felt supported and were able to receive answers to their queries through an email account specifically created for that purpose. We found no evidence of a similar channel being used in other studies. Another interesting fact worth mentioning is the predominant female sex in this study, as in others carried out among patients with rare diseases [19].

5. Conclusions

Patients with rare diseases are a population group who have high healthcare requirements, and health services have been deeply affected by the pandemic. Therefore, health status and psychological wellbeing of these patients have also been affected.

As the results presented above suggest, levels of depression and anxiety may have been influenced by the current pandemic state as levels of moderate or severe anxiety were higher in patients with rare diseases than in those with other types of chronic diseases and the general population, as it is found in 26% of the study population. Additionally, the percentage of patients with moderate or severe depression (30%) among patients with rare diseases during the pandemic nearly doubled the percentage of those affected in the general population during the same period. However, comparing the results to those of a 2019 study in patients with rare diseases, the levels remained at similar levels prior to and during the pandemic. This study found that symptoms such as anxiety and depression have a higher prevalence among women than men. The uncertainty surrounding the pandemic may increase anxiety and depression, as the patients with higher levels of symptoms are those who had family members or close friends who had been ill or passed away due to COVID-19, more so than those who were ill themselves. The study results indicate that during the pandemic, anxiety/depression remained at a higher level in this group than in the general population.

Depression and anxiety in patients with rare diseases is an issue that needs further research, as there are not many publications that consider rare diseases as a whole. There are several articles on certain specific diseases, but none including patients with rare diseases in general.

Supplementary Materials: Participants accessed and completed the questionnaires through the online form link: https://docs.google.com/forms/d/e/1FAIpQLSdJ2woR6VTxl7LRt8-B1uTBrvHMaF0_mChMMhxqsi2bYWiw9A/viewform?usp=sf_link.

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MATERIAL SUPLEMENTARIO CAPÍTULO I

Cuestionario sobre EERR + COVID-19

Mediante la selección de la casilla "SI, doy mi consentimiento" , está usted dando su consentimiento para participar anónima y voluntariamente en el proyecto de investigación denominado "Cuidados a pacientes con EERR frente al COVID-19".

El objetivo de este estudio será investigar si ha aumentado la frecuencia de depresión y ansiedad en esta población heterogénea la situación originada por la pandemia debida al SARS-CoV-2.

En el caso que usted quisiera conocer los resultados de los cuestionarios, y debido a que es anónimo, al final tiene habilitada una casilla en la que usted indicará un código (el que usted determine) y si quiere saber el resultado del cuestionario nos puede enviar un e-mail a la dirección de correo electrónico del proyecto (proyecto.eerr.covid19@gmail.com) indicando el código que usted haya indicado y solicitando los datos de los cuestionarios realizados. Si en dicha casilla no indica un código no se podrán asociar los datos a usted y no le podremos enviar sus resultados.

*Obligatorio

1. *

Selecciona todos los que correspondan.

- [ ] Si, doy mi consentimiento

2. ¿Mayor de 18 años? *

Marca solo un óvalo.

- ( ) Si

3. ¿Ha presentado síntomas de ansiedad o depresión en los meses previos a la pandemia por COVID-19? *

Entendiéndose por síntomas de ansiedad, tanto síntomas mentales; preocupación constante, cansancio, irritabilidad y problemas para concentrarse y conciliar el sueño. Como síntomas físicos; pulsaciones elevadas, sudoración excesiva, tensión muscular, temblores, mareos, desmayos. Y como síntomas de depresión; estado de ánimo irritable o bajo la mayoría de las veces, dificultad para conciliar el sueño o exceso de sueño, cambio grande en el apetito (a menudo con aumento o pérdida de peso), cansancio y falta de energía, sentimientos de inutilidad, odio a sí mismo y culpa, dificultad para concentrarse, movimientos lentos o rápidos, inactividad y retraimiento de las actividades usuales, sentimientos de desesperanza o abandono, pensamientos repetitivos de muerte o suicidio, pérdida de placer en actividades que suelen hacerlo feliz, incluso la actividad sexual.

Marca solo un óvalo.

- ◯ Si
- ◯ No

Datos antropométricos

Le rogamos rellene los datos de la forma más clara posible, indicando lo que se le pregunta.

4. Fecha de nacimiento *

_____

Ejemplo: 7 de enero del 2019

5. País de nacimiento *

_____

6. País de residencia *

_____

7. Ciudad de residencia *

_____

8. Sexo *

Marca solo un óvalo.

- ◯ Hombre
- ◯ Mujer

9. Estado civil *

Marca solo un óvalo.

- ◯ Soltero/a
- ◯ Casado/a
- ◯ Divorciado/a o Separado/a
- ◯ Otro: _____

10. Peso en kg *

_____

11. Talla en cm *

_____

12. Profesión actual *

_____

13. Nivel de estudios alcanzados *

Marca solo un óvalo.

- ◯ Sin estudios
- ◯ Educación General Básica - EGB
- ◯ Educación Secundaria Obligatoria - ESO
- ◯ Bachillerato / Ciclos Medios de Formación Profesional (FP)
- ◯ Ciclos Superiores de Formación Profesional (FP)
- ◯ Universitarios
- ◯ Otros

14. Enfermedad Rara que le han diagnosticado *

_____

15. English diagnosis *

Marca solo un óvalo.

- ◯ Sí
- ◯ No

16. Centro Sanitario en el que fue diagnosticado/a *

_____

17. Consumo actual de tabaco *

Selecciona todos los que correspondan.

- ☐ Si
- ☐ No

18. Consumo actual de alcohol *

Selecciona todos los que correspondan.

- [ ] Si
- [ ] No

Aspectos relacionados al COVID-19

19. ¿Ha estado usted enfermo por COVID-19? *

Marca solo un óvalo.

- ◯ Sí
- ◯ No

20. Si usted enfermó por COVID-19, ¿qué tipo de paciente fue?

Marca solo un óvalo.

- ◯ Sintomático
- ◯ Asintomático

21. Si usted enfermó por COVID-19, ¿necesitó ingreso en hospital?

Marca solo un óvalo.

- ◯ Si
- ◯ No

22. If you were ill with from COVID-19, please indicate the symptoms you had, regardless of the duration of such symptoms. You may indicate several symptoms.

Selecciona todos los que correspondan.

- [ ] Fever
- [ ] Dry cough
- [ ] Breathlessness
- [ ] Tiredness
- [ ] Odynophagia, pain in the posterior pharynx with or without swallowing
- [ ] Anosmia, total loss of smell
- [ ] Ageusia, total loss of taste
- [ ] Muscular pain
- [ ] Diarrhea
- [ ] Chest pain
- [ ] Headache
- [ ] No symptom, I was asymptomatic

23. Si usted NO enfermó por COVID-19, ¿ha sido contacto estrecho de alguna persona que ha enfermado por COVID-19?. Se entiende por caso estrecho aquel que ha requerido un seguimiento por vigilancia epidemiológica y que ha tenido que hacer cuarentena de 10 días al menos. *

Marca solo un óvalo.

- ◯ Sí
- ◯ No

24. ¿Ha tenido usted familiares o amigos cercanos enfermos con COVID-19, que no conviven con usted, por los que usted no tuvo que hacer cuarentena? *

Marca solo un óvalo.

- ◯ Sí
- ◯ No
- ◯ Otro: _____

25. ¿Tiene usted familiares o amigos cercanos fallecidos por COVID-19? *

Marca solo un óvalo.

- Sí
- No

CUESTIONARIO SOBRE LA SALUD DEL PACIENTE-9 (PHQ-9)

Con esta herramienta pretendemos conocer como ha afectado la pandemia originada por el coronavirus SARS-CoV-2 en su estado de salud mental. Si la situación de confinamiento ha originado algún grado de depresión en usted.

Durante las últimas 2 semanas, ¿qué tan seguido le han afectado cualquiera de los siguientes problemas?(Marque con una "✓" para indicar su respuesta)

26. 1. Poco interés o placer en hacer las cosas

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

27. 2. Se ha sentido decaído(a), deprimido(a), o sin esperanzas

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

28. 3. Dificultad para dormir o permanecer dormido(a), o hadormido demasiado

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

29. 4. Se ha sentido cansado(a) o con poca energía

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

30. 5. Con poco apetito o ha comido en exceso

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

31. 6. Se ha sentido mal con usted mismo(a) – o que es unfracaso o que ha quedado mal con usted mismo(a) o consu familia

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

32. 7. Ha tenido dificultad para concentrarse en cosas tales comoleer el periódico o ver televisión

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

33. 8. ¿Se ha estado moviendo o hablando tan lento que otraspersonas podrían notarlo?, o por el contrario – ha estadotan inquieto(a) o agitado(a), que se ha estado moviendomucho más de lo normal

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

34. 9. Ha pensado que estaría mejor muerto(a) o se le ha ocurridolastimarse de alguna manera

Marca solo un óvalo.

- Para nada
- Varios días
- Más de la mitad de los días
- Casi todos los días

35. Si usted marcó cualquiera de estos problemas, ¿qué tan difícil fue hacer su trabajo, las tareas delhogar o llevarse bien con otras personas debido a tales problemas?

Marca solo un óvalo.

- Para nada difícil
- Un poco difícil
- Muy difícil
- Extremadamente difícil

Escala del Trastorno de Ansiedad Generalizada (GAD-7)

Con esta herramienta pretendemos conocer como ha afectado la pandemia originada por el coronavirus SARS-CoV-2 en su estado de salud mental. Si la situación de confinamiento ha originado algún grado de ansiedad en usted.

Las siguientes frases describen problemas que usted puede haber padecido. Recapacite sobre las
ocasiones en que los ha sufrido durante las 2 últimas semanas, e indique cual de las 4 opciones
describe mejor la frecuencia con la que se ha enfrentado a esos problemas.

36. 1. Sentirse nervioso, ansioso, notar que se le ponen los nervios de punta

Marca solo un óvalo.

- Nunca
- Varios días
- La mitad de los días
- Casi cada día

37. 2. No ser capaz de parar o controlar sus preocupaciones

Marca solo un óvalo.

- Nunca
- Varios días
- La mitad de los días
- Casi cada día

38. 3. Preocuparse demasiado sobre diferentes cosas

Marca solo un óvalo.

- Nunca
- Varios días
- La mitad de los días
- Casi cada día

39. 4. Dificultad para relajarse

Marca solo un óvalo.

- Nunca
- Varios días
- La mitad de los días
- Casi cada día

40. 5. Estar tan desasosegado que le resulta difícil parar quieto

Marca solo un óvalo.

- Nunca
- Varios días
- La mitad de los días
- Casi cada día

41. 6. Sentirse fácilmente disgustado o irritable

Marca solo un óvalo.

- Nunca
- Varios días
- La mitad de los días
- Casi cada día

42. 7. Sentirse asustado como si algo horrible pudiese pasar

Marca solo un óvalo.

- Nunca
- Varios días
- La mitad de los días
- Casi cada día

Código para recibir el cuestionario.

Le recordamos que en el caso que usted quisiera conocer los resultados de los cuestionarios, y debido a que es anónimo, usted puede indicar un código (el que usted determine) en la siguiente casilla.

Posteriormente envíe un correo electrónico al siguiente buzón: proyecto.eerr.covid19@gmail.com, en el que indique el código que usted haya indicado, y mediante el cual solicite los datos del cuestionario que ha realizado.

Rellenar la casilla no es obligatoria, en caso que no la rellene no se podrán asociar los datos a usted y no le podremos enviar sus resultados.

43. Código para recibir el cuestionario

Este trabajo se engloba dentro de un proyecto más amplio que busca dar visibilidad sobre las Enfermedades Raras.

Nuestra intención es publicar todos aquellos problemas relacionados con la salud, que afectan directamente a los pacientes que presentan Enfermedades Raras.
Aunque esta encuesta es totalmente anónima, en el caso que usted haya enfermado por COVID-19, y quiere publicar como fue su caso, le pedimos que se ponga en contacto con el correo electrónico:

proyecto.eerr.covid19@gmail.com

Indique su "Código para recibir el cuestionario" del apartado anterior y escriba explícitamente que "Quiere publicar su caso relacionado con el COVID-19".

Nos pondremos en contacto con usted lo antes posible.

GRACIAS a todos los que habéis colaborado en esta encuesta que tiene como objetivo el dar a conocer al mundo las dificultades que presenta una persona diagnosticada con una Enfermedad Rara.

Sección sin título

CAPÍTULO II

A continuación, se abordó el segundo objetivo específico. Se realizó una revisión sistemática de la literatura sobre el Síndrome de Hajdu-Cheney para obtener la información necesaria y establecer el punto de partida del estudio del síndrome.

Se redactó una revisión sistemática en forma de artículo con los datos recogidos, el cual fue publicado con el título:

Hajdu–Cheney Syndrome: A Systematic Review of the Literature.

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Review

Hajdu–Cheney Syndrome: A Systematic Review of the Literature

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Abstract: Hajdu–Cheney syndrome (HCS) is a rare genetic disease that causes acroosteolysis and generalized osteoporosis, accompanied by a series of developmental skeletal disorders and multiple clinical and radiological manifestations. It has an autosomal dominant inheritance, although there are several sporadic non-hereditary cases. The gene that has been associated with Hajdu-Cheney syndrome is *NOTCH2*. The described phenotype and clinical signs and symptoms are many, varied, and evolve over time. As few as 50 cases of this disease, for which there is currently no curative treatment, have been reported to date. The main objective of this systematic review was to evaluate the results obtained in research regarding Hajdu–Cheney Syndrome. The findings are reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and were registered on the web PROSPERO under the registration number CRD42020164377. A bibliographic search was carried out using the online databases Orphanet, PubMed, and Scielo; articles from other open access sources were also considered. Finally, 76 articles were included, and after their analysis, we have obtained a series of hypotheses as results that will support further studies on this matter.

Keywords: Hajdu–Cheney syndrome; acroosteolysis; receptor; *NOTCH2*; connective tissue; rare diseases

1. Introduction

1.1. Rationale

Hajdu–Cheney syndrome (HCS) is a rare genetic disease of the connective tissue that belongs to the osteolysis syndromes group [1]. It is registered in the OMIM (Mendelian Inheritance in Man) project database with reference #102500 and in ORPHANET under the reference ORPHA955. It is also known as acro-dento-osteo dysplasia, acroosteolysis with osteoporosis and changes in the skull and mandible, arthrodentoosteodysplasia, and serpentine fibula-polycystic kidney syndrome. The prevalence [2] of this disease is less than one person in one million (<1/1,000,000) and it is caused by a heterozygotic mutation of gene *NOTCH2* [3] located on chromosome 1p13-p11. HCS follows an

autosomal-dominant inheritance pattern, although descriptions of cases with sporadic mutations can be found [4].

The disease was first described in 1948 by N. Hajdu [5] and later completed by D. Cheney in 1965 [6]. Since then, around 50 [6] cases of patients with HCS have been reported and, in general, all patients show a case of osteolysis of the distal phalanges and generalized osteoporosis, accompanied by other disorders, such as craniofacial and skeletal dysmorphia, developmental skeletal disorders, premature loss of teeth, and a short stature [7].

Due to the variability in the expression of *NOTCH2*, patients can be found with phenotypic differences between them. Furthermore, this disease presents a wide and specific clinical spectrum that is rare to encounter in full in a single patient. Therefore, reports are found of cases diagnosed with HCS presenting variable clinical manifestations that worsen over time due to their age-dependent progression, with changes from early infancy to late adulthood [8].

1.2. Objectives

The main objective of this systematic review was to evaluate the results obtained in research regarding Hajdu–Cheney syndrome and to provide a report that guarantees a starting point for future studies with greater complexity on this matter. The secondary objectives of this study were to investigate the different phenotypes described and to enunciate a clinical description of HCS, to obtain up-to-date information on HCS to understand the impact of this disease on affected patients, and to evaluate possible future healthcare interventions.

2. Materials and Methods

2.1. Protocol and Registration

The method followed for this report was a systematic review of scientific literature published regarding Hajdu–Cheney syndrome in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which consist of a 27-item checklist of the most important sections of an original article, as well as a flow diagram that depicts the flow of information through the different phases of a systematic review.

This systematic review was conducted following a protocol and was registered on the web PROSPERO [9] (registration number CRD42020164377).

2.2. Eligibility Criteria

We selected only original articles published prior to July 2020 that provided information on HCS, without restrictions regarding the language of publication or publication date. Previous bibliographic reviews were not accepted, nor articles that were exclusively case reports.

2.3. Information Sources and Search

We searched the Orphanet, PubMed, and Scielo databases. We also manually searched the reference lists of included articles to find other relevant articles.

The chosen structured language was obtained from MeSH (Medical Subject Headings) terms and Health Sciences Descriptors (DeCS). The descriptors used were "Hajdu-Cheney Syndrome", "Acro-Osteolysis", "Receptor, *NOTCH2*", "Connective tissue", and "Rare diseases", and the boolean operators used were "AND" and "OR".

The search chains used are shown in Table 1.

Table 1. Search chains used.

Information Source	Search Chain
ORPHANET	Código ORPHA: 955
PUBMED	((((Hajdu-Cheney Syndrome) OR (Acro-Osteolysis)) OR (Receptor, *NOTCH2*)) OR (Connective tissue)) OR (Rare diseases) (((((((“hajdu-cheney syndrome”[MeSH Terms] OR (“hajdu cheney”[All Fields] AND “syndrome”[All Fields])) OR “hajdu cheney syndrome”[All Fields]) OR ((“hajdu”[All Fields] AND “cheney”[All Fields]) AND “syndrome”[All Fields])) OR “hajdu cheney syndrome”[All Fields]) OR (((“acro-osteolysis”[MeSH Terms] OR “acro osteolysis”[All Fields]) OR (“acro”[All Fields] AND “osteolysis”[All Fields])) OR “acro osteolysis”[All Fields])) OR ((((“receptor, *NOTCH2*”[MeSH Terms] OR (“receptor”[All Fields] AND “*NOTCH2*”[All Fields])) OR “*NOTCH2* receptor”[All Fields]) OR (“receptor”[All Fields] AND “*NOTCH2*”[All Fields])) OR “receptor *NOTCH2*”[All Fields])) OR ((“connective tissue”[MeSH Terms] OR (“connective”[All Fields] AND “tissue”[All Fields])) OR “connective tissue”[All Fields])) OR ((“rare diseases”[MeSH Terms] OR (“rare”[All Fields] AND “diseases”[All Fields])) OR “rare diseases”[All Fields])
SCIELO	(Hajdu-Cheney Syndrome) OR (Acro-Osteolysis) OR (Receptor, *NOTCH2*)

2.4. Data Collection Process

All articles found were transferred to the web application Mendeley using the Mendeley web importer tool.

After importing all the articles to the Mendeley website, we organized them by folders according to the database from which each article had been retrieved and subsequently classified them in sub-folders according to thematic blocks. Finally, we proceeded to eliminate all duplicates, therefore achieving the definitive list for our study.

2.5. Study Selection

After searching the different databases, we proceeded to eliminate duplicate documents. Following the removal of duplicates, we screened all the retrieved articles by title and abstracts to identify those that fit the inclusion criteria. Next, we independently read each article, focusing on its methodology to verify whether it complied with our eligibility criteria and all articles that did not were discarded.

Three independent reviewers completed this phase of the selection process. Any disagreements were discussed with the study supervisor and resolved via a consensus-based discussion.

This study selection process is explained in more detail in the results section.

2.6. Data Collection Process and Data Items

We prepared a data extraction form, drew three papers one by one, modified our form after each draw, and finally developed the definitive data extraction form we used for the remaining articles. Three independent revisors extracted the data of each article. A discussion was held between the revisors to reach a consensus each time there was a disagreement on any data extracted. If the three revisors could not reach an agreement, the study supervisor was consulted.

The data items extracted included the surname of the first author, year of publication, study title, thematic block, and results. Due to the vast amount of reported studies, we divided the articles into four thematic blocks: disease genetics, description of the disease and evolution of phenotype, diagnosis and differential diagnosis, and treatment.

2.7. Synthesis of the Results

Considering the information this review provides, we have obtained a series of hypotheses as results that will support further, more complex studies on this matter. Alongside providing a complete analysis of this disorder, we confirmed that this syndrome, and rare diseases in general, belong to an

area of medicine in which there is still much to explore, and the advancement of scientific knowledge is needed in order to progress.

3. Results

3.1. Study Selection

Figure 1 shows the flow diagram of the articles assessed during the production of this systematic review.

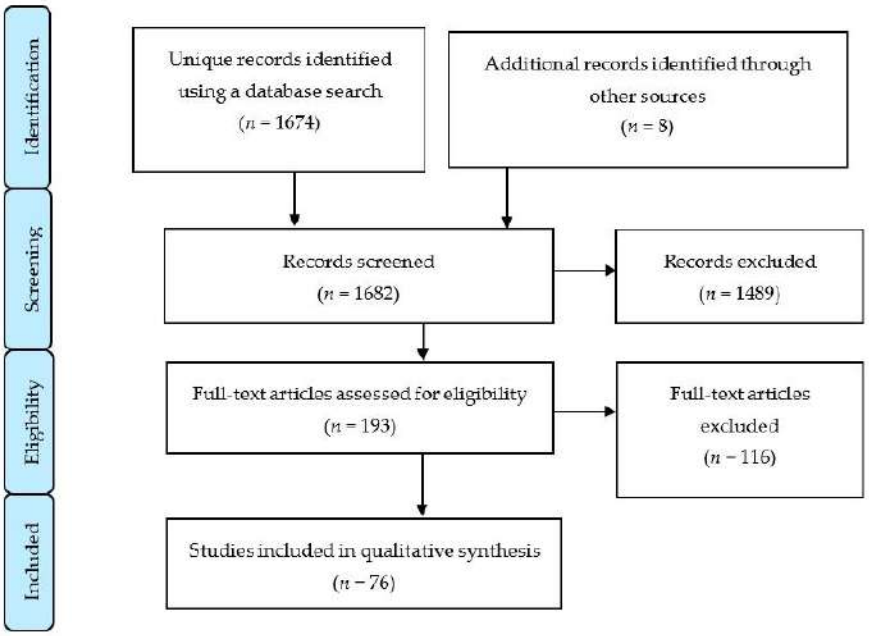

Figure 1. Flow diagram.

Of the 193 articles assessed for eligibility, 117 articles were excluded, amongst which were systematic reviews, duplicate articles, and some that were exclusively case reports.

As we mentioned previously, we divided the articles into four thematic blocks: disease genetics, description of the disease and evolution of phenotype, diagnosis and differential diagnosis, and treatments.

We now present the results of the selected studies.

Table 2 shows a summary of the results of the most remarkable studies of this revision, divided by thematic block. Additionally, we include a supplementary table where the objectives, results, sample, and demographic region are shown for all 76 articles included in this systematic review (Supplementary Table S1).

Table 2. Summary of the results of the most remarkable studies of this revision, divided by thematic block.

Authors	Article	Thematic Block	Results
Gibofsky [10] (1987)	Genetics of the Hajdu–Cheney Syndrome	Disease genetics	The existing association between *NOTCH* and Hajdu–Cheney syndrome (HCS), focusing on the signaling pathway and other disorders caused by *NOTCH* mutations.
Le Caignec [11] (2011)	Pathologies humaines et récepteurs *NOTCH*		
Zanotti et al. [12] (2012)	*NOTCH* regulation of bone development and remodeling and related skeletal disorders.		
Canalis et al. [13] (2005)	The fate of circulating osteoblasts		
Canalis et al. [14] (2016)	Hajdu Cheney mouse mutants exhibit osteopenia, increased osteoclastogenesis, and bone resorption		
Ramos et al. [15] (1998)	Further evidence that the Hajdu-Cheney Syndrome and the "Serpentine Fibula-Polycystic Kidney Syndrome" are a single entity	Description of the disease and evolution of the phenotype	Descriptions of the clinical manifestations of the disease, highlighting its variable phenotype, the wide spectrum of clinical presentation, and the age-dependent progression and possible complications. Resolution of the controversy between serpentine fibula-polycystic kidney syndrome and HCS, proving it is only another manifestation of HCS, not an independent disorder as was previously believed.
Nunziata et al. [16] (1990)	High turnover osteoporosis in acro-osteolysis (Hajdu-Cheney Syndrome)		
Brown et al. [7] (1976)	The acro-osteolysis syndrome: morphologic and biochemical studies		
Brennan et al. [8] (2001)	Hajdu-Cheney Syndrome: evolution of phenotype and clinical problems		
Siklar et al. [17] (2000)	Hajdu-Cheney Syndrome with growth hormone deficiency and neuropathy		
Barakat et al. [18] (1996)	Kidney abnormalities in Hajdu-Cheney Syndrome		
Ades et al. [19] (1993)	Hydrocephalus in Hajdu-Cheney Syndrome		
Currarino [20] (2009)	Hajdu-Cheney Syndrome associated with serpentine fibulae and polycystic kidney disease		

Table 2. *Cont.*

Authors	Article	Thematic Block	Results
Isidor et al. [21] (2011)	Truncating mutations in the last exon of *NOTCH2* cause a rare skeletal disorder with osteoporosis		
Gray et al. [22] (2012)	Serpentine fibula polycystic kidney syndrome is part of the phenotypic spectrum of Hajdu–Cheney Syndrome		
Kawamura et al. [23] (1991)	Hajdu-Cheney Syndrome: MR imaging	Diagnosis and differential diagnosis	We establish the necessary conditions for a diagnostic orientation toward HCS and propose several related disorders that are useful for a differential diagnosis.
O'Reilly et al. [24] (1994)	Hajdu-Cheney Syndrome		
Singh et al. [1] (2003)	Talo-patello-scaphoid osteolysis, synovitis, and short fourth metacarpals in sisters: A new syndrome?		
Gripp et al. [25] (2011)	Lateral meningocele syndrome and Hajdu–Cheney Syndrome: different disorders with overlapping phenotypes		
Sawin et al. [26] (1997)	Basilar invagination in osteogenesis imperfecta and related osteochondrodysplasias: medical and surgical management		
Ornetti et al. [27] (2012)	Osteoporotic compression fracture revealing Hajdu-Cheney Syndrome	Treatment	There is no curative treatment. There are several studies on bisphosphonates, although there is no clear evidence of their effectiveness. Surgical intervention to prevent complications is effective in certain cases. The current treatment of HCS is focused on the management of complications and underlying problems to improve the quality of life and life expectancy.
Murtagh-Schaffer et al. [28] (2008)	Spinal reconstruction in Hajdu-Cheney Syndrome		
Schawo et al. [29] (2006)	Junge frau mit rückenschmerzen und akroosteolysen		
McKiernan et al. [30] (2007)	Integrated anti-remodeling and anabolic therapy for the osteoporosis of Hajdu–Cheney Syndrome		
Sakka et al. [31] (2017)	Bone structural characteristics and response to bisphosphonate treatment in children with Hajdu-Cheney Syndrome		

3.2. Disease Genetics

Studies on the genetics of HCS are intimately related to the etiology of the disease, as Gibofsky [10] predicted in his study, by suspecting that the inheritance of this disease would be autosomal dominant and caused by a genetic mutation. Years later, these facts were confirmed by Simpson et al. [3] when they established that HCS is caused by a mutation on *NOTCH2*. Authors, such as Caignec [11], studied the genetics of *NOTCH* (structure, function, and signaling processes) and their relation to bone development and homeostasis in depth. They also identified mutations on *NOTCH* that are related to other disorders. Engin et al. [32] focused on the link between the *NOTCH* signaling pathway and bone development, and obtained among their results that the loss of *NOTCH* signaling correlates with an increase in osteoporosis levels. Sahlgren et al. [33] centered their projects on stem cell differentiation via the *NOTCH* signaling pathway. The study by Canalis et al. published in 2005 [13] presented the bone remodeling process involved in normal bone development, and in their 2016 study [14], they present the creation and development of a mouse model of HCS after the introduction of a mutation 6955C3T in *NOTCH2*. The heterozygotic mutant mice show shorter femurs, smaller dimensions, cancellous bones, and increased bone resorption. In 2012, Zanotti et al. [12] studied bone development in HCS, highlighting the importance of *NOTCH* in these processes and the fact that mutations on this gene lead to a loss of bone mass and acroosteolysis. In 2014, Zanotti et al. [34] further managed to inactivate *NOTCH* signaling by crossing homozygotic mice with mice where the promoter osterix governs the expression of Cre, while in 2018 [35], they presented their mouse model of HCS (*NOTCH2*tm1.1Ecan) to study the link between the disease and osteoarthritis. Vollersen et al. [36] developed a mouse model of HCS by introducing a pathogenic mutation (6272delT) on the murine gene *NOTCH2*. Changes in bone density, acroosteolysis, and an increase in the osteoblast-osteoclast index were found when compared to control cases.

3.3. Description of the Disease and Evolution of the Phenotype

Studying and describing the evolution of the phenotype in HCS is a highly complex task. Hajdu et al. [5] carried out the first description of the disease by presenting the case of a patient with craniofacial alterations. In his report, Cheney [6] completed the description by adding a series of clinical manifestations that accompanied cranial dysplasia. Since then, many authors have offered their contributions to this matter. Brennan et al. [8], Regev et al. [37], and Jirečková et al. [38] confirmed and justified in their studies that the disease has three main features: phenotypic variability, a wide spectrum of clinical presentation, and an age-dependent progression. Majewski et al. [39] confirmed that HCS is a hereditary disease, although sporadic cases do exist, as Descartes et al. [4] report in their study. The description of the disease is continually growing as it is directly linked to the appearance and reporting of new cases. Brown et al. [7] carry out a complete description of the disease, affirming that these patients present with low bone density and deficient bone formation. Rosenmann et al. [40], Elias et al. [41], Bruckner et al. [42], Letchumanan et al. [43], Stathopoulos et al. [44], and Nunziata et al. [16] argue that the most prevalent signs in HCS are acroosteolysis and generalized osteoporosis. Hoey et al.'s [45] study stands out as it reports a case with intrauterine fractures, as do the studies of Barakat et al. [18] and Battelino et al. [46], who remark renal alterations as their main result; Siklar's [17] contribution regarding growth hormone and its relation to short stature in patients with HCS and Herscovici et al.'s [47] study presenting cervical instability as a sign of the disease also stand out. We must also note the studies of Bazopoulou-Kyrkanidou et al. [48] and Antoniades et al. [49], which focus on dental anomalies. Fryns's [50] study discusses alterations in voice and speech, and Avela et al. [51] present the case of a patient with severe dural ectasia as a sign of HCS. The existence of multiple fractures, in the case of Mannstadt et al. [52], reaffirms what other authors believed on this matter. Amalnath et al. [53] mention micrognathia as another characteristic of HCS throughout his study. Another three remarkable groups in this thematic block are Takafumi et al. [54] and their case of premature ovarian failure; Sargin et al. [55], who mention congenital cardiovascular alterations; Swan et al. [56], who confirm that HCS can also cause congenital alterations of the ocular system with the results of their study.

Beyond the simple clinical manifestations, we can also find possible complications of the disease that must be included in its description. It is worth mentioning syringomyelia, as studied by Nishimura et al. [57] and Tanimoto et al. [58]. Due to thoracic deformities, breathing complications can develop, as Sasaki et al. [59] expose in their study. Ades et al. [19] and Takatani et al. [60] focus most of their studies on hydrocephalus as a complication of HCS, and the possible neurological damage is described by various authors, such as Niijima et al. [61].

There are studies on the past controversy between serpentine fibula-polycystic kidney syndrome and HCS. Several authors, such as Fryns et al. [62], Ramos et al. [15], Currarino et al. [20], Isidor et al. [21], and Gray et al. [22] published their studies to show that serpentine fibula-polycystic kidney syndrome is not an independent disease from HCS but instead another manifestation of the same disease, as both are caused by the same mutation.

3.4. Diagnosis and Differential Diagnosis

It is complicated to reach a definite and early diagnosis of HCS. Studies, such as Schawo's [29], reveal that physical appearance and radiological testing will guide the diagnostic process, although the final confirmation must be genetic. Kawamura et al. [23] indicate the importance of performing magnetic resonance imaging as a complementary test to physical examination. Damian et al. [63] proposed capillaroscopy as a clinical test for HCS diagnosis.

Brennan and Pauli [8] created a diagnostic tool that establishes inclusion criteria for this syndrome based on a series of physiological parameters and genetic inheritance based on the London Dysmorphology Database. This tool facilitates the diagnosis of HCS by focusing on a series of clinical manifestations, such as acroosteolysis, wormian bones or open sutures, platybasia, premature denture loss, micrognatia, coarse face, coarse hair, midfacial flattening, short stature (<5%), and a documented positive family history. It establishes differences between adults and children due to its age-dependent progression and changes in phenotype.

For adults, three options are proposed that would lead to a positive diagnosis:

- Acroosteolysis plus three clinical manifestations, except for a documented positive family history.
- Acroosteolysis plus a documented positive family history.
- Documented positive family history plus two other manifestations, except for acroosteolysis.

For children, two options are proposed:

- Four clinical manifestations, except for a documented positive family history.
- Documented positive family history plus two manifestations.

There are studies on the differential diagnosis of HCS, as it can often resemble other diseases when trying to establish a diagnosis. Sawin et al. [26] state that basilar invagination is not a sign that is unique to HCS. Singh et al. [1] describe similarities between HCS and other acroosteolysis syndromes. In their 2011 and 2015 studies, Gripp et al. [25,64] explain that lateral meningocele, despite its clinical links with HCS, is not the same disease. O'Reilly et al. [24] point to scleroderma and sarcoidosis as disorders that also cause acroosteolysis, and therefore, the importance of including them in a correct differential diagnosis. Another remarkable study on differential diagnosis is that of Albano et al. [65] since it establishes the differences between serpentine fibula, Melnick–Needles, and HCS.

3.5. Treatment

In the search for an efficient treatment for HCS, there are two major aspects: pharmacological and surgical treatments.

Relevant studies on pharmacological treatments for HCS include that by Sakka et al. [31], who worked on a therapy that uses bisphosphonates and found oscillations in bone mineral density indexes of the lumbar spine. At the beginning of the study, the values decreased, then increased in response to treatment, but the effect did not persist after its interruption. Pittaway et al. [66] also

studied bisphophonates but obtained different results for each patient that were dependent on age. Adami et al. [67] tried obtaining an increase in bone mineral density with denosumab but acroosteolysis persisted. Tsinopoulou et al. [68] and Al-Mayouf et al. [69] experimented with pamidronate without achieving a curative result. Hwang et al. [70] tried to slow down the process of bone degradation using zoledronic acid, and in 2007 and 2008, McKiernan et al. [30,71] carried out a pharmacological study to treat osteoporosis in HCS with an anti-resorption and anabolic therapy.

When analyzing the surgical aspect, we found studies focused on the treatment of complications of HCS, such as cervical kyphotic deformities in patients with osteoporosis by Mattei et al. [72], dental restorations by Vingerhoedt et al. [73] and Liljeström et al. [74], spinal reconstruction by de Murtagh-Schaffer et al. [28], and translation of the radius by Fujioka et al. [75] and Ornetti et al. [27], who were able to treat a vertebral compression fracture surgically. It is also worth mentioning the studies of Yamaguchi et al. [76] and August et al. [77] on anesthesia and specific treatment indications for patients with HCS prior to surgery, as well as the study on post-surgical analgesia for pain management by Zietz et al. [78].

Despite significant advances in treatment, the results of the evaluated studies on this matter indicate that a curative treatment for HCS does not yet exist.

4. Discussion

4.1. Summary of Evidence

We now present a general description of the disease.

4.1.1. Epidemiology

Hajdu–Cheney syndrome has a prevalence of less than 1 in 1,000,000 live births [2]. Since 1948, approximately 50 [3] cases have been described worldwide. It is a genetic disease with autosomal-dominant inheritance [39], although sporadic cases have been reported [4].

4.1.2. Etiology

As we have previously stated, HCS is a genetic disease caused by a heterozygotic mutation of *NOTCH2*. The *NOTCH* signaling pathway [11] is constituted by a series of linked occurrences that are intimately related to skeletal development and homeostasis [32]; therefore, alterations of this pathway cause disorders in both processes.

NOTCH receptors are transmembrane proteins [11] that have three major parts: an extracellular domain that consists of multiple EGF (epidermal growth factor)-like repeats, another intermembrane domain, and an intracellular one that consists of multiple ankyrin repeats, nuclear localization signals, and a proline-, glutamic acid-, serine-, and threonine-rich domain, known as the PEST domain, whose function is the recycling of proteins. *NOTCH* has four receptors (*NOTCH* 1, 2, 3, and 4) and five ligands (JAG1, JAG2, and DLL 1, 2, and 4).

The *NOTCH* signaling pathway activates when a cell's ligand adheres to the receptor of the cell, provoking the separation of the intracellular domain, which travels to the nucleus of the cell where it begins to complete its function.

In HCS, there is a truncation in exon 34 of *NOTCH2* [22], which causes a protein product to be missing the PEST domain, leading to an elevated level of *NOTCH* signaling activity in multiple tissues, therefore altering the usual process. This has a noticeable impact on skeletal development and homeostasis, leading to the disease.

Several disorders have been associated with *NOTCH* mutations along with HCS [11]:

- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy): mutations of EGF-like repeats of *NOTCH3*.
- Bicuspid aortic valve: protein-truncating mutations of *NOTCH1*.

- LAL-T: protein-truncating mutations of the PEST domain of *NOTCH1*.
- Alagille syndrome: mutation of the splice acceptor of exon 33 of *NOTCH2*.

4.1.3. Pathophysiology

Once a mutation has occurred, normal skeletal development is affected, causing a series of skeletal anomalies. There is a bone density deficit [7] that leads to generalized skeletal dysplasia. Osteoporosis is one of the most characteristic signs of HCS, along with acroosteolysis of distal phalanges, both of which are caused by a series of local mechanisms [16] that increase osteoclastic activity and impact bone formation negatively. Congenital defects in ossification can be found in fetal cartilage [7], causing peripheral dysostosis that worsens the acroosteolysis.

Understanding these processes helps us to comprehend some of the clinical manifestations that are seen in the wide spectrum of clinical presentations this syndrome provides: fractures in long bones due to bone demineralization [52], frequent respiratory infections caused by thoracic deformities and ventilatory restriction [24], basilar invagination [19] and its neurological alterations, and short stature due to vertebral collapse. These are some of the clinical complications that arise from these processes that, when considered alongside the age-dependent progression of HCS, make this syndrome so complex.

4.1.4. Clinical Manifestations

This syndrome has three major characteristics regarding symptoms: a variable phenotype [37], a wide spectrum of clinical presentation [8], and an age-dependent progression [38]. Following these three parameters, some patients are diagnosed with HCS with different clinical presentations and phenotypic differences person to person, and these manifestations tend to evolve over time. The following clinical manifestations are the most representative of HCS:

- Cranial alterations: bathrocephaly, presence of multiple wormian bones, delayed suture closure, thickened dome of the skull, absent frontal sinuses, elongated sella turcica, small jaw, basilar invagination, dolichocephaly, and occipital prominence.
- Facial alterations: coarse and dysmorphic facies, elongated philtrum, micrognathia, low-set ears, telecanthus, sinofridia, bushy eyebrows, long eyelashes, wide nose, high arched palate, premature denture loss, jaw malocclusion, hirsutism, and hypertelorism.
- Musculoskeletal alterations: short stature, short neck, fractures of long bones, joint laxity, biconcave vertebrae, kyphoscoliosis, cervical instability, vertebral collapse, genu valgum, serpentine fibula, acroosteolysis, pseudoclubbing, short fingers, Hippocratic fingers, progressive distal bone resorption, bone demineralization, osteopenia, and osteoporosis.
- Cardiovascular alterations: congenital heart disease, patent arterial duct, and sept defects.
- Digestive alterations: intestinal malrotation.
- Neurological alterations: hydrocephalus and lateral meningocele.
- Renal alterations: hypospadias, cryptorchidism, renal cysts, and kidney failure.
- Respiratory alterations: thoracic deformities, ventilatory restriction, and recurrent infections.
- Other alterations: delayed motor development, hearing loss, changes of the voice, deep voice, short nails, plantar ulcers, and hernias.

The most relevant clinical manifestations are shown in Figures 2–5.

Figure 2. (**A**) Photograph of a patient's face. (**B**) Lateral photograph of a patient's head and face. The following are noted: small face, telecanthus and downslated palpebral fissures, micrognathia, small mouth, thin lips, long philtrum and full cheeks, low-positioned ears with a crease in the lobules, short neck, and coarse hair.

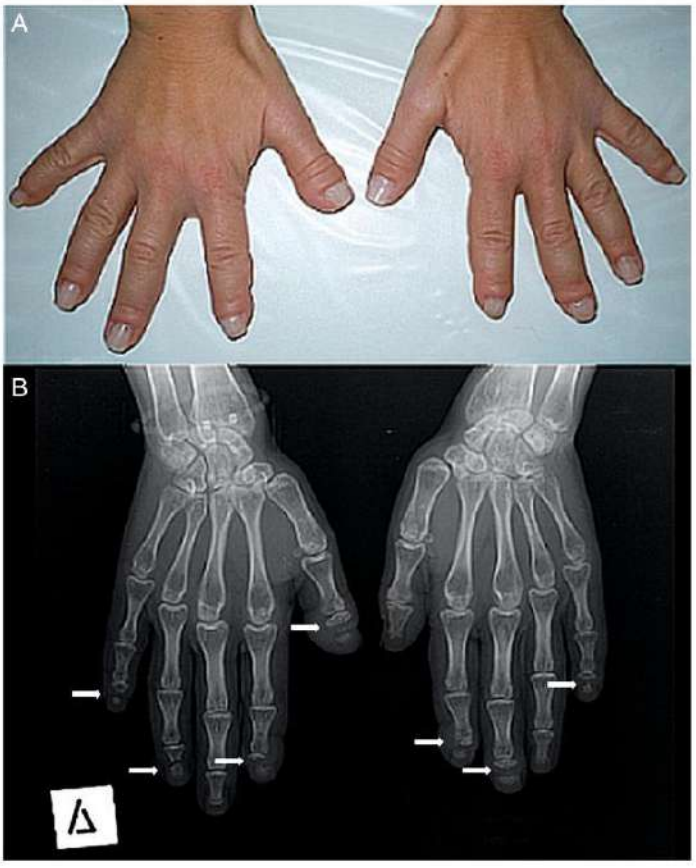

Figure 3. (**A**) Photograph of a patient's hands. Many of her fingers are thick (predominately the right thumb) with pseudo-clubbing. (**B**) Anteroposterior radiograph of a patient's hands. Osteolysis of the distal phalanges is found in most of the fingers (only the left thumb, the left fourth, and the right third fingers have a normal appearance). In all lesions, osteolysis has a transverse pattern across the width of the terminal phalanx (white arrows).

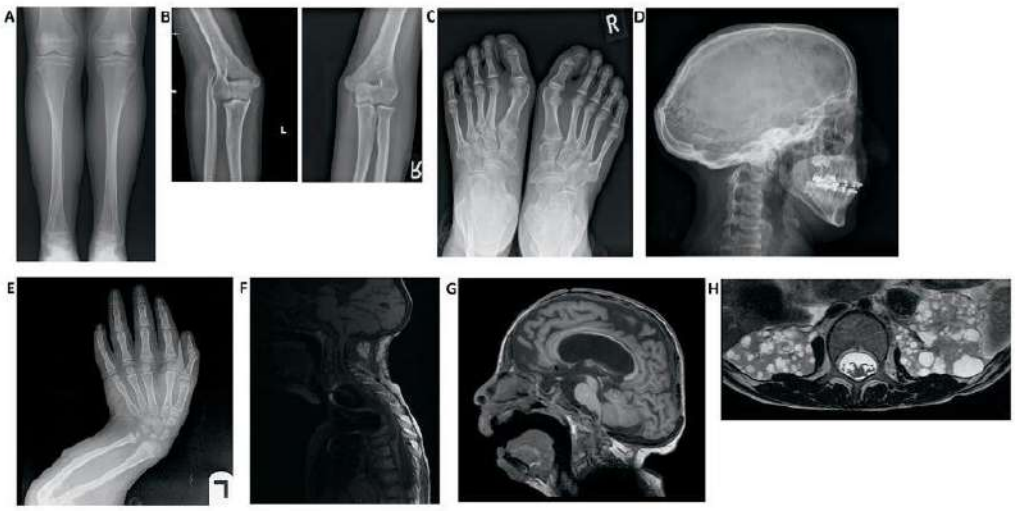

Figure 4. Imaging findings in patients with Hajdu–Cheney syndrome. (**A**) Radiograph of the frontal view of the tibia and fibula. Note the elongated and medially deviated fibula, superposing the tibia bone, referred to as a "serpentine fibula". (**B**) Radiographs of the lateral view of the left arm showing dislocation of the radial head. (**C**) Radiograph of the frontal view of the feet showing hallux valgus, crowded metatarsal bones, short foot distal digits, and acroosteolysis signs at distal phalanges of the first digit. (**D**) Radiograph of the lateral view of the skull, demonstrating batrocephaly, frontal sinuses hypoplasia, and multiple occipital wormian bones. (E) Radiograph of the frontal view of the hands, showing crowded metacarpal bones, short hand distal digits, and acroosteolysis signs at the distal phalanges. (E) Radiograph of the lateral view of the arm, showing shortening of the distal fingers and long bones of the arm, and a curved radius and ulna. (**F**) Spinal MRI showing deformations of the cervical spine, as well as a significant syrinx of the cord. (**G**) Brain MRI. Note the ventricular enlargement with a VP (ventriculo-peritoneal) shunt, frontal hypoplasia of the sinuses, and a small foramen magnum. (**H**) Abdominal MRI showing multiple bilateral kidney cysts.

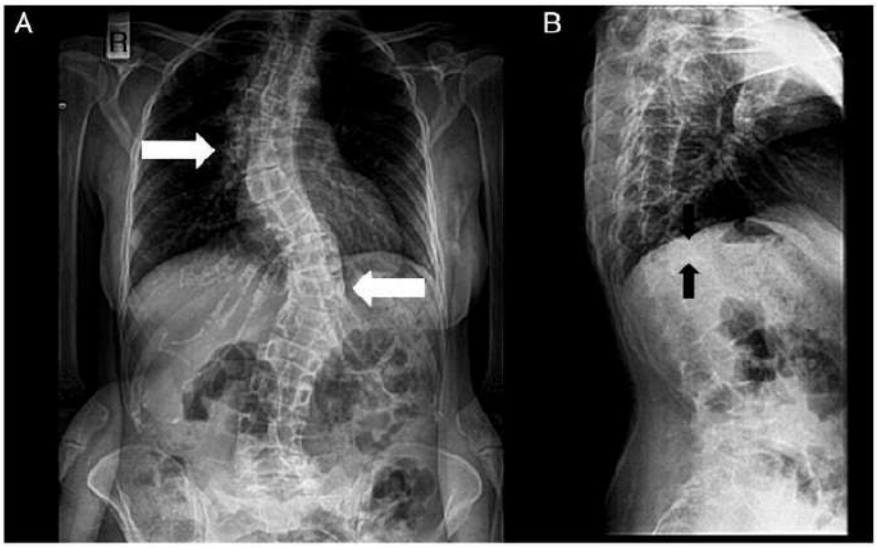

Figure 5. Radiographs of a patient's spine. (**A**) Anteroposterior view. (**B**) Lateral view. The following are noted: scoliosis (double major—with a right thoracic and a left thoracolumbar curve—white arrows), and biconcave deformities of the upper and lower endplate (fishbone deformity—black arrows) of many vertebrae and decreased bone density.

The most frequent clinical complications in this syndrome are basilar invagination, and consequently, brain damage, hydrocephalus [19], syringomyelia [57], vertebral collapse due to compression [27], and ventilatory restriction caused by a thoracic deformity [24].

There is a subgroup of patients within this syndrome that present two distinctive signs: serpentine fibula and polycystic kidneys. Initially, it was thought that patients with these signs belonged to a separate disease [65], different from HCS, but genetic studies demonstrated both originate from the same mutated gene [15]. The variable expression of *NOTCH2* justifies the frequent association of serpentine fibula and polycystic kidneys as nothing but another manifestation of HCS and not an independent syndrome [22].

Based on the age-dependent progression of this syndrome, it has been shown that after monitoring several cases over time, the phenotypes and symptoms gradually worsen. There are a series of stages of the disease according to age, allowing for seven generational divisions [8]:

- birth (<1 year old)
- early childhood (ages 1–5)
- childhood (ages 6–12)
- adolescence (ages 13–19)
- early adulthood (ages 20–33)
- middle adulthood (ages 36–65)
- late adulthood (65+).

We highlight the importance of presenting an updated report of the variability of manifestations and the changing phenotype of this disease.

4.1.5. Diagnosis

The diagnosis of HCS is suspected via the observation of physical appearance and radiological findings [29], but the final diagnosis is reached via genetic sequencing of exon 34 of *NOTCH2*.

Brennan and Pauli [8] created a diagnostic tool that establishes the inclusion criteria for this syndrome.

It is worth highlighting the need for establishing a differential diagnosis with other disorders and syndromes that share clinical manifestations and could generate diagnostic uncertainty.

Regarding its osteolytic nature [1], HCS can be compared to some of the disorders that belong to the group of osteolysis syndromes, such as Torg, François, Whyte–Hemingway, Winchester, and a new syndrome known as Talo-patello-scaphoid osteolysis, synovitis, and short fourth metacarpals. One of the main characteristics of the disease to be analyzed is acroosteolysis but we can also find other disorders that present as signs, such as scleroderma, sarcoidosis, neuropathic disorders, and rheumatoid syndromes [24]. Progeria and pycnodysostosis are another type of disorder that cause congenital acroosteolysis. Including Paget's disease or other osteoporosis syndromes in the differential diagnosis is also of interest due to their osteoporotic nature. There are studies on the differential diagnosis between HCS and lateral meningocele considering phenotypic similarities [25,64] and with Alagille syndrome because of their genetic links. Other syndromes that share basilar invagination [26] amongst their clinical manifestations are osteogenesis imperfecta, congenital osteochondrodysplasia, and spondyloepiphyseal dysplasia, and could also be considered when creating the differential diagnosis for HCS.

4.1.6. Treatment

There is no definitive or effective pharmacological treatment for HCS at present, and although certain trials with bisphosphonates have been developed [30], there is insufficient evidence of their effectiveness. Surgical intervention as a method to avoid complications has proven to be effective in certain cases [28]. The current treatment for HCS is based on the management of complications and underlying problems in order to improve the patient's quality of life and life expectancy. Certain

studies consider the manipulation of gamma-secretase inhibitors as a possible way to prevent this disorder [11].

4.1.7. Prognosis

HCS is classified as a rare genetic disease but there are no studies that offer a global perspective on the prognosis and quality of life of affected patients. The severity of the disease depends on the affected organs, clinical complications, and the degenerative evolution of each patient. The generalized osteoporosis and the development of acroosteolysis will cause fractures, difficulty with walking, and dependency for everyday life activities.

The prognosis worsens when complications such as basilar invagination exist, causing neurologic alterations, or thoracic deformities that cause ventilatory restriction. Due to the low prevalence and the lack of qualitative information about this syndrome, it is difficult to know the burden of disease and the years of healthy life lost. Researchers should discuss the results and how they can be interpreted given previous studies and the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

4.2. Limitations

Despite the fact that undeniable progress has been made by the scientific community regarding this syndrome at present (its genetic origin is known, there is a general understanding of the processes that lead to disease development, and that there is ongoing research to further understand this disorder), the management of HCS is still based on the treatment of the different clinical complications that arise and on the evaluation of the individual needs of each patient to provide care that improves their quality of life.

Due to the low prevalence of HCS and the number of reported cases, obtaining a complete description and global perspective of the disorder is complex. The geographical dispersion of the reported cases, the time between them, a lack of constant monitoring of identified cases, and the absence of specific descriptive protocols for this disorder are some of the obstacles that hinder the development of research into this syndrome.

An early and definitive diagnosis of HCS is not an easy task, mainly due to the vast amount of clinical manifestations of the disease, phenotypic differences between cases, and the evolution of manifestations over time. When the wide range of disorders and syndromes with overlapping clinical signs and symptoms that lead to diagnostic uncertainty is also considered, the diagnosis of HCS proves challenging.

4.3. Possible Future Lines of Research

As in all rare diseases without treatment, the best option is to improve patients' quality of life as much as possible. The establishment of a specific multidisciplinary intervention plan would be of great help for the everyday lives of these patients. To do so, it would be essential to:

- Revise all the cases described in the literature and describe new cases to obtain a large and reliable sample of patients with HCS with whom a descriptive study could be carried out. Such a study would serve not only to identify the cases of this disorder and study its prevalence but also to analyze the complete phenotype of HCS in depth, allowing for a greater understanding of this syndrome and contribute to an earlier diagnosis in new cases.
- Standardize protocols for the evaluation of signs and symptoms, diagnostic orientation, and disease management. Action protocols and specific intervention plans are basic and necessary tools for the universalization of care for patients with HCS. The use of a nursing methodology and its taxonomy NANDA (North American Nursing Diagnosis Association) - NIC (Nursing Interventions Classification) - NOC (Nursing Outcomes Classification) would provide a universal, individualized, and multidisciplinary approach to this disorder.

- Perform a qualitative study on HCS to understand the impact on the quality of life and daily activities. Such a study would aim to report on the level of dependency and adaptation of these patients and evaluate possible future healthcare interventions.

5. Conclusions

Considering the scientific and clinical variance of HCS, there is a need for standardization and universalization of the evaluation and diagnostic testing to simplify and facilitate progress in the research setting. A detailed description of cases would improve the diagnosis timing, quality of treatment, and overall assistance of each patient.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/17/6174/s1, Table S1: Objectives, results, sample and demographic region shown for all 76 articles.

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MATERIAL SUPLEMENTARIO CAPÍTULO II

AUTHOR	ARTICLE	OBJETIVES	RESULTS	SAMPLE	DEMOGRAPHIC REGION
		Disease Genetics			
Gibofsky (9)(1987)	Genetics of the Hajdu-Cheney syndrome.	To present basic aspects of HCS genetics.	Theoretical approach to the origins of HCS. Initial evidence of HCS having autosomal dominant inheritance.	-	New York (United States of America)
Canalis et al.(12) (2005)	The fate of circulating osteoblasts.	To present processes involved in normal bone physiology.	Complete description of the bone remodelling process.	-	Connecticut (United States of America)
Sahlgren et al.(32) (2006)	*NOTCH* signaling and its integration with other signaling mechanisms.	To study stem cell differentiation via the *NOTCH* signalling pathway.	Highlights the importance of *NOTCH* in the destination of steam cells, cellular differentiation in several organs and its integration with other signalling pathways.	-	Stockholm (Sweden)
Engin et al. (31)(2008)	Dimorphic effects of *NOTCH* signaling in bone homeostasis.	To study the link between the *NOTCH* signalling pathway and abnormal bone development.	The specific increase in osteoblast with *NOTCH* function causes severe osteosclerosis due to a higher proliferation of immature osteoblasts. However, the loss of all the *NOTCH* signalling in osteoblasts is associated to osteoporosis.	-	Houston (United States of America)
Simpson et al.(3) (2011)	Mutations in *NOTCH*2 cause Hajdu-Cheney syndrome, a disorder of severe and progressive bone loss.	To understand the genetic origin of HCS.	Identification of mutations on *NOTCH*2 that cause HCS.	14	London (United Kingdom)
Caignec(10) (2011)	Pathologies humaines et récepteurs *NOTCH*.	To study the *NOTCH* signalling pathway.	Development of the genetics of *NOTCH* (structure, function and signalling processes) and to identification of *NOTCH* mutations and their respective diseases.	-	Nantes (France)
Zanotti et al. (11)(2012)	*NOTCH* regulation of bone development and remodeling and related skeletal disorders.	To study abnormal bone development in HCS.	*NOTCH* is key in the regulation of bone development. *NOTCH* mutations have a negative impact causing bone loss and acroosteolysis,	-	Connecticut (United States of America)

Zanotti et al.(33) (2014)	*NOTCH*1 and *NOTCH*2 expression in osteoblast precursors regulates femoral microarchitecture.	To study the expression of *NOTCH* in osteoblast in mouse models.	They crossed homozygotic mice with mice where the promoter *osterix* governs the expression of *Cre* to inactivate *NOTCH* signalling and analyse bone parameters.	-	Connecticut (United States of America)
Canalis et al. (13)(2016)	Hajdu-Cheney mouse mutants exhibit osteopenia, increased osteoclastogenesis, and bone resorption.	Presentation of the mouse model of HCS.	Creation and development of a HCS mouse model by introducing a mutation 6955C3T on *NOTCH*2.	-	Connecticut (United States of America)
Zanotti et al. (34)(2018)	Mice harboring a Hajdu Cheney Syndrome mutation are sensitized to osteoarthritis.	To study the link between HCS and osteoarthritis in the mouse model.	The mouse model of the disease (*NOTCH*2tm1.1Ecan) confirmed its sensitivity to development of osteoarthritis in unstable joints.	-	Connecticut (United States of America)
Vollersen et al. (35) (2018)	High Bone Turnover in Mice Carrying a Pathogenic *NOTCH*2 Mutation Causing Hajdu-Cheney Syndrome.	To analyse the role of *NOTCH*2 in bone remodelling.	Development of a mouse model for HCS by introducing a pathogenic mutation (6272delT) in the murine gene *NOTCH*2. Changes in bone density, acroosteolysis and an increase in the osteoblast-osteoclast index were found when compared to control cases.	-	Hamburg (Germany)
		Description of the disease and evolution of phenotype			
Hajdu (5)(1948)	Cranio-skeletal dysplasia.	Presentation of a new syndrome	First description and definition of HCS.	1	Prague (Czech Republic)
Cheney W. (6)(1965)	Acro-Osteolysis.	To develop and define HCS as a disease.	Complete definition of HCS.	5	Michigan (United States of America)
Brown et al.(7) (1976)	The acro-osteolysis syndrome: Morphologic and biochemical studies.	To study HCS at a clinical and biochemical level.	Description of the clinical presentation of HCS. Presentation, description and comparison of two new cases with those previously described at a clinical and biochemical level.	2	Minneapolis (United States of America)

Elias et al.(40) (1978)	Hereditary osteodysplasia with acro-osteolysis (the Hajdu-Cheney syndrome).	Presentation of two cases of HCS	Description of two cases where a bone biopsy o fan affected area was performed that showed that a neurovascular dysfunction and local liberation of osteolytic mediators may be involved in the pathogenics of this disorder.	2	Siracusa (Italy)
Rosenmann et al.(39) (1979)	Sporadic idiopathic acro-osteolysis with cranio-skeletal dysplasia, polycystic kidneys and glomerulonephritis A case of the Hajdu-Cheney syndrome.	Presentation of a case of HCS.	Description of a case of HCS with acroosteolysis, craniofacial alterations and renal alterations.	1	Jerusalem (Israel)
Hoey et al. (44)(1983)	Hajdu-Cheney syndrome associated with intrauterine fractures and arachnoid cysts	Presentation of a case of HCS.	Description of a case of HCS, highlighting a cranial deformity due to multiple fractures prior to birth.	1	London (United Kingdom)
Niijima et al. (60)(1984)	Familial osteodysplasia associated with trigeminal neuralgia: Case report.	Presentation of a case of HCS.	Description of the first case of HCS that presents with trigeminal neuralgia requiring surgical treatment.	1	Kyoto (Japan)
Herscovici et al.(46) (1990)	Cervical instability as an unusual manifestation of Hajdu-Cheney syndrome of acroosteolysis.	Presentation of a case of HCS.	Description of a case of HCS with skeletal alterations that include cervical instability.	1	London (United Kingdom)
Nunziata et al.(15) (1990)	High turnover osteoporosis in acro-osteolysis (Hajdu-Cheney syndrome).	To study the existing link between physiopathology and phenotype in HCS.	Confirmation regarding acroosteolysis and osteoporosis caused by a series of localized action mechanisms stimulating osteoclastic resorption. Report of one case.	1	Naples (Italy)
Ades et al. (18)(1993)	Hydrocephalus in Hajdu-Cheney syndrome.	To inform of possible complications of HCS.	Presentation, through the description of a case, of one of the possible complications of HCS: basilar invagination.	1	Adelaide (Australia)

Barakat et al. (17)(1996)	Kidney abnormalities in Hajdu-Cheney syndrome	To analyse kidney alterations in HCS.	The importance of reviewing kidney diseases to establish a complete diagnosis of patients with HCS. Renal insufficiency, vesicoureteral reflux, cystic disease, glomerulonephritis, chronic kidney disease and hypertension may be warning signs during childhood for early diagnosis. Presentation of a case.	1	Saudi Arabia
Tanimoto et al. (57)(1996)	Syringomyelia associated with Hajdu-Cheney syndrome: Case report.	Presentation of a case of HCS.	Description of a case of HCS with neurological alterations caused by syringomyelia requiring surgical treatment.	1	Kobe (Japan)
Nishimura et al.(56) (1996)	Syringohydromyelia in Hajdu-Cheney syndrome	Presentation of a case of HCS.	Description of a case where syringomyelia appears as a complication of HCS.	1	Tokyo (Japan)
Fryns (61)(1997)	Serpentine fibula syndrome: a variant clinical presentation of Hajdu-Cheney syndrome?	Analysis of the controversy between HCS and SFPCK.	First notions that both syndromes may actually be the same clinical entity.	-	Leuven (Belgium)
Sawin et al.(25) (1997)	Basilar invagination in osteogenesis imperfecta and related osteochondrodysplasias: Medical and surgical management.	To perform a study on basilar invagination as a clinical complication of diseases belonging to osteogenesis imperfecta group.	Analysis of basilar invagination as a complication of certain bone diseases, the possible treatments and response to them before, during and after. The study is carried out with a sample of 25 cases, of which 4 have HCS.	25	Iowa (United States of America)
Ramos et al. (1998)(14)	Further evidence that the Hajdu-Cheney syndrome and the serpentine fibula-polycystic kidney syndrome are a single entity	To establish that HCS and SFPCK (Serpentine fibula-polycystic kidney syndrome) constitute the same syndrome.	Revision and comparison of the cases describe in the literature both for HCS and SFPCK. Confirmation that both syndromes belong to the same entity.	55	Zaragoza (Spain)

Leidig-Bruckner et al. (41)(1999)	Severe osteoporosis in familial Hajdu-Cheney syndrome: Progression of acro-osteolysis and osteoporosis during long-term follow-up.	Analysis of the evolution of HCS over time in two patients.	HCS is a degenerative disease. The clinical finding found in both cases evolve negatively with the passing of time.	2	Heidelberg (Germany)
Siklar et al. (16)(2000)	Hajdu-Cheney syndrome with growth hormone deficiency and neuropathy	To study the existing link between short stature and neurophysiological problems with the HCS phenotype.	Inclusion in the HCS phenotype of the deficit of growth hormone and the presence of peripheral motor neuropathies. Presentation of a case.	1	Ankara (Turkey)
Brennan et al. (8)(2001)	Hajdu–Cheney syndrome: evolution of phenotype and clinical problems.	To establish a complete definition of HCS phenotype.	HCS presents a variable phenotype, a wide spectrum of clinical presentation and age-dependent progression. Tool for the inclusive diagnosis of HCS.	6	Wisconsin (United States of America)
Antoniades et al.(48) (2003)	Hajdu-Cheney syndrome (acro-osteolysis): A case report of dental interest.	Presentation of a case of HCS.	Description of a case of HCS that required surgical treatment of the oral cavity due to skeletal alterations.	1	Tesalonica (Grece)
Bazopoulou-Kyrkanidou et al.(47) (2007)	Periodontitis associated with Hajdu-Cheney Syndrome	Presentation of a case of HCS.	Description of a case of HCS with alterations of the oral cavity and premature denture loss, a sign related to HCS phenotype.	1	Athens (Grece)
Fryns et al. (49)(2008)	Vocal cord paralysis and cystic kidney disease in Hajdu-Cheney syndrome	Presentation of a case of HCS.	Description of a case of HCS with respiratory alterations and vocal cord paralysis.	1	Leuven (Belgium)
Letchumanan et al.(42) (2009)	A patient with progressive shortening of the fingers.	Presentation of a case of HCS.	Description of a case that highlights acroosteolysis as a significant signo f HCS phenotype.	1	Malasya
Currarino(19) (2009)	Hajdu-Cheney syndrome associated with serpentine fibulae and polycystic kidney disease	To study the existing link between HCS and SFPCK.	Revision and comparison of the cases of HCS and SFPCK described to date. Presentation of a case. Inclusion of new signs in the HCS phenotype.	1	Dallas (United States of America)

Isidor et al. (20)(2011)	Truncating mutations in the last exon of *NOTCH*2 cause a rare skeletal disorder with osteoporosis	Analysis of the link between HCS, SFPCK, Alagille syndrome and Melnick Needles ay a genetic and clinical level.	Confirmation that the mutations that cause these disorders belong to different genes. Presentation of a case. Comparison of two cases of HCS with another of the different syndromes.	1	Nantes (France)
Majewski et al.(38) (2011)	Mutations in *NOTCH*2 in families with Hajdu-Cheney syndrome	To study the origin of HCS.	Genetic sequencing of the sample and the obtained results confirm that HCS is caused by a mutation on *NOTCH*2.	Cohort 7 families	Quebec (Canada)
Avela et al. (50)(2011)	Hajdu-Cheney syndrome with severe dural ectasia.	Presentation of a case of HCS.	Description and evolution of a case of HCS with severe dural ectasia	1	Helsinki (Finland)
Nozaki et al.(53) (2012)	A girl with Hajdu-Cheney syndrome and premature ovarian failure.	Presentation of a case of HCS.	Description of a case of HCS that presents premature ovarian failure as a possible complication of the disease.	1	Fukuoka (Japan)
Gray et al. (21)(2012)	Serpentine fibula polycystic kidney syndrome is part of the phenotypic spectrum of Hajdu-Cheney syndrome.	To study the controversy between SFPCK and HCS	Insists that SFPCK simply another sign of HCS. Both answer to the same mutation of *NOTCH*2. Presentation of two cases.	2	Dunedin (New Zeland)
Stathopoulos et al. (43)(2013)	Severe osteoporosis and mutation in *NOTCH*2 gene in a woman with Hajdu-Cheney syndrome	Presentation of a case of HCS.	Description of a case of HCS that presents most of the clinical and radiological findings. The genetic diagnosis is established, confirming the link between HCS and *NOTCH*2.	1	Athens (Grece)
Sargin et al.(54) (2013)	Hajdu-Cheney syndrome with ventricular septal defect.	Presentation of a case of HCS.	Description of a case of HCS with cardiac alterations and plantar ulcers.	1	Aydin (Turkey)
Mannstadt et al. (51)(2014)	A 27-year-old man with severe osteoporosis and multiple bone fractures.	Presentation of a case of HCS.	Description of a case that presents fractures and osteoporosis but etiology is unknown.	1	Boston (United States of America)
Descartes et al.(4) (2014)	Hajdu-Cheney syndrome: Phenotypical progression with de-novo *NOTCH*2 mutation.	To study the phenotype of HCS.	Description of a clinical case. Confirmation that the HCS phenotype has an age-dependant progression.	1	Birmingham (United Kingdom)

Battelino et al.(45) (2016)	End-Stage Renal Disease in an Infant With Hajdu-Cheney Syndrome.	Presentation of a case of HCS.	Description of a case of HCS with kidney abnormalities. First case of HCS with renal failure during childhood.	1	Liubliana (Slovenia)
Deepak et al.(52) (2016)	Hajdu-Cheney syndrome - A rare cause of micrognathia.	Presentation of a case of HCS.	Description of a case of HCS with evident micrognatia and acroosteolysis.	1	Puducherry (India)
Jirečková et al.(37) (2018)	The Age Dependent Progression of Hajdu-Cheney Syndrome in Two Families.	To analyse the evolution of phenotype and clinical presentation of HCS according to age.	Description of two cases of HCS from two different families. Highlights one of the most remarkable characteristics of HCS: age-dependant progression.	2	Prague (Czech Republic)
Swan et al.(55) (2018)	Congenital Glaucoma: a Novel Ocular Manifestation of Hajdu-Cheney Syndrome.	Presentation of a case of HCS.	Description of a case of HCS with visual alterations. First case where congenital glaucoma is presented as a sign.	1	Brisbane (Australia)
Sasaki et al. (58)(2019)	Fatal case of Hajdu-Cheney syndrome with idiopathic pulmonary hemosiderosis	Presentation of a case of HCS.	Description of a case of HCS with respiratory alterations and a remarkable sign of idiopathic pulmonary hemosiderosis.	1	Hachinohe (Japan)
Takatani et al. (59)(2019)	Hajdu-Cheney syndrome: Infantile onset of hydrocephalus and serpentine fibulae	Presentation of a case of HCS.	Description of a case of HCS that present from early age with hydrocephalus and platybasia, clinical finding identified by MRI. Another remarkable sign of this case is serpentine fibula, reinforcing the link between SF and HCS.	1	Chiba (Japan)
Regev et al. (36)(2019)	Phenotype variability in Hajdu-Cheney syndrome.	To study the phenotype variability through two cases.	Description of two cases of HCS with two different phenotypes. Confirmation that HCS presents a variable expression of the same mutated gene.	2	Tel-Hashomer (Israel)
Diagnosis and Differential Diagnosis					

Kawamura et al.(22) (1991)	Hajdu-Cheney Syndrome: MR imaging. Neuroradiology.	To carry out the surveillance of a previously describe case of HCS 10 years after by using MRI as a diagnostic tool.	Revision of a previously described case. Evaluation of new radiological findings detected by MRI. Confirmation that the HCS phenotype presents an age-dependant progression.	1	Tenri (Japan)
O'Reilly et al.(23) (1994)	Hajdu-Cheney syndrome.	To establish a differential diagnosis for HCS.	Presentation of a case focusing on the differential diagnosis of HCS with other disorders such as sclerodermia, sarcoidosis and progeria, among others.	1	London (United Kingdom)
Singh et al. (1)(2003)	Talo-patello-scaphoid osteolysis, synovitis, and short fourth metacarpals in sisters: A new syndrome?	Presentation of a new osteolytic syndrome	Description of clinical cases. Differential diagnosis of this new syndrome and other osteolytic syndromes.	2	Minnesota (United States of America)
Schawo et al. (28)(2006)	Junge frau mit rückenschmerzen und akroosteolysen. Radiologe.	Presentation of a case and to inform on the diagnosis of HCS.	Presentation of a case. Clinical orientation to the diagnosis of HCS is based on physical appearance and radiological findings.	1	Heidelberg (Germany)
Albano et al.(64) (2007)	Phenotypic overlap in Melnick-Needles, serpentine fibula-polycystic kidney and Hajdu-Cheney syndromes: A clinical and molecular study in three patients.	To establish the differential diagnosis between Melnick-Needles, HCS and SFPCK.	Differential diagnosis of HCS and the other two syndromes through the description of three cases. Confirmation is obtained of HCS and SFPCK belonging to the same syndrome and that the mutations that cause them are on the same gene. Melnick-Needles, however, is a different disorder as it is cause by a mutation on FLNA.	3	São Paulo (Brasil)
Gripp ..(24) (2011)	Lateral meningocele syndrome and Hajdu-Cheney syndrome: Different disorders with overlapping phenotypes.	To study the differential diagnosis between HCS and lateral meningocele.	Authors perform a comparative study between HCS and lateral meningocele by analysing previously described cases.	-	Wilmington (United States of America)

Gripp et al.(63) (2015)	Truncating mutations in the last exon of *NOTCH*3 cause lateral meningocele syndrome	Genetic and clinical analysis of lateral meningocele syndrome	Description and comparison of five cases and approach to the differential diagnosis with HCS.	5	Philadelphia (United States of America)
Damian et al.(62) (2016)	Capillaroscopic findings in a case of Hajdu-Cheney syndrome	To present capilaroscopy ad a diagnostic tool in HCS.	Description of the first case of HCS where capilaroscopic findings are seen. Capilaroscopy as a tool for early diagnosis.	1	Cluj-Napoca (Rumania)
		Treatment			
Liljeström et al. (73)(2003)	Occlusal rehabilitation of a patient with hereditary multicentric osteolysis.	Presentation of a case of HCS.	Description of a case with HCS who required dental restauration.	1	Turku (Finland)
Al-Mayouf et al.(68) (2006)	Cyclic intravenous pamidronate treatment in children with nodulosis, arthropathy and osteolysis syndrome	To analyse the use of pamidronate as a treatment for osteolytic syndromes.	Description of seven cases and their response to pamidronate as a pharmacological treatment.	7	Riyadh (Saudi Arabia)
McKiernan. (29) (2007)	Integrated anti-remodeling and anabolic therapy for the osteoporosis of Hajdu-Cheney syndrome	Presentation of a case of HCS who underwent pharmacological treatment.	Description of a case of HCS who was treated pharmacologically for osteoporosis with an anti-remodelling and anabolic therapy. Results obtained suggest dissociation of bone formation.	1	Marshfield (United States of America)
Murtagh et al. (27)(2008)	Spinal reconstruction in Hajdu-Cheney syndrome.	Presentation of a case previously described in 1978 who now receives surgical treatment.	Highlights the importance of surgical treatment in patients with HCS who require spinal reconstruction, an effective although aggressive technique.	1	Siracusa (Italy)
McKiernan. (70) (2008)	Integrated anti-remodeling and anabolic therapy for the osteoporosis of Hajdu-Cheney syndrome: 2-Year follow-up	Evaluation and surveillance of treatment of osteoporosis initiated two years earlier.	After two years of this treatment, the result found is that biochemical markers of bone turnover present an increase in bone resorption and in osteolysis.	1	Marshfield (United States of America)
August et al. (76)(2009)	Anesthesia for a child with Hajdu-Cheney syndrome	To study the use of anesthesia in HCS. Presentation of a case of HCS.	Description of a case of HCS that required surgical treatment and needed anesthesia.	1	Sacramento (United States of America)

Vingerhoedt et al.(72) (2010)	Syndrome of Hajdu-Cheney: Three case reports of orofacial interest.	Presentation of three cases of HCS.	Description of three cases of HCS with alterations of the mouth and dentures.	3	Leuven (Belgium)
Hwang et al.(69) (2011)	Effect of Zoledronic Acid on Acro-Osteolysis and Osteoporosis in a Patient with Hajdu-Cheney Syndrome	To understand the effect of Zoledronic Acid as a treatment for HCS.	Description of a case of HCS who underwent treatment with Zoledronic Acid. Results show that this anti-resorption therapy may favour osteoporosis but not acroosteolysis.	1	Yonsei (South Korea)
Tsinopoulou et al. (67)(2012)	Two-year cyclic infusion of pamidronate improves bone mass density and eliminates risk of fractures in a girl with osteoporosis due to Hajdu-Cheney syndrome	Presentation of a case of HCS.	Description of a case of HCS who received pharmacological treatment with pamidronate.	1	Athens (Grece)
Ornetti et al. (26)(2012)	Osteoporotic compression fracture revealing Hajdu-Cheney syndrome.	Presentation of a case who underwent surgical treatment.	Analysis of a case of HCS with medullar collapse and the surgical intervention.	1	Dijon (France)
Fujioka et al.(74) (2013)	Proximal translation of the radius following arthroplasty of the distal radioulnar joint in Hajdu-Cheney syndrome	Presentation of a case of HCS.	Description of a case with HCS who underwent surgical treatment.	1	Kobe (Japan)
Yamaguchi et al.(75) (2013)	A case report of anesthesia for a child with Hajdu-Cheney syndrome	To study the use of anesthersi in HCS. Presentation of a case of HCS.	Description of a case with HCS who required surgical treatment and needed anesthesia.	1	Tomishiro (Japan)
Zietz et al. (77)(2013)	Continuous spinal labor analgesia in a patient with Hajdu-Cheney syndrome	Presentation of a case of HCS.	Description of a case of HCS and the use of post-surgical analgesia for pain management.	1	Toronto (Canada)
Mattei et al. (71)(2015)	Surgical challenges in the management of cervical kyphotic deformity in patients with severe osteoporosis: an illustrative case of a patient with Hajdu–Cheney syndrome	Presentation of a case of HCS.	Description of a case of HCS that required surgical intervention due to cervical skeletal alterations.	1	Buffalo (United States of America)
Adami et al. (66)(2016)	Hajdu Cheney Syndrome; report of a novel *NOTCH*2 mutation and treatment with denosumab.	Presentation of a case of HCS and response to denosumab as a pharmacological treatment.	Description of a case of HCS treated denosumab, obtaining an increase in bone mineral density but a negative progression of acroosteolysis.	1	Verona (Italy)

Sakka et al.(30) (2017)	Bone Structural Characteristics and Response to Bisphosphonate Treatment in Children with Hajdu-Cheney Syndrome	To analyse the bone response in HCS to pharmacological treatment with bisphosphonates.	Description of five cases treated with bisphosphonates. Bone mineral density of the lumbar spine decreased at the beginning of the study and increased in response to treatment, an effect that did not persist after interruption of treatment.	5	Birmingham (United Kingdom)
Pittaway et al. (65)(2018)	Bisphosphonate therapy for spinal osteoporosis in Hajdu-Cheney syndrome.	To establish and evaluate the efficacy of bisphosphonate therapy as a pharmacological treatment for HCS.	Despite the increase in bone mineral density after the administration of treatment, the results obtained show that response is variable in each patient and age-dependant	15	London (United Kingdom)

Tabla de resultados de la revisión sistemática

CAPÍTULO III

El tercer objetivo específico se realizó con la descripción de dos casos nuevos diagnosticados del Síndrome de Hajdu-Cheney.

Dentro de la dificultad de poder describir un caso de una enfermedad considerada ultra-rara, con el trabajo de difusión realizado a través de autores y asociaciones de personas con enfermedades raras, se han podido describir dos casos no antes descritos en la literatura científica. Uno de una mujer adulta y otro un caso pediátrico.

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Case Report

Hajdu-Cheney Syndrome: Report of a Case in Spain

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Abstract: This paper describes the case of a 54-year-old woman diagnosed with Hajdu–Cheney syndrome, who presents with characteristic craniofacial dysmorphia, short stature, premature loss of teeth, developmental skeletal disorders, fibrocystic mastopathy, bilateral hearing loss and an intermittent mild neutropenia. The patient received treatment with bisphosphonates and was awaiting evaluation for surgical arthroplasty of both hips when she suffered a motor vehicle accident, which led to a rapid progression in her disease by increasing her degree of dependence for most activities of daily living. The clinical presentation and radiologic findings seen in this case confirm the three main features of the syndrome: phenotypic variability, an age-dependent progression and the presence of generalized osteoporosis and acroosteolysis of distal phalanges. The main objective of the manuscript is to describe a new case of a patient diagnosed with Hajdu–Cheney syndrome. Due to the low prevalence of the syndrome and the small number of cases reported in the scientific literature, obtaining a complete description and a global perspective of the disease is complex.

Keywords: Hajdu-Cheney syndrome; rare diseases; acroosteolysis; osteoporosis; bone re-sorption

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1. Introduction

Hajdu-Cheney syndrome (HCS) is a rare genetic disease. It is registered in the database of the OMIM project with reference number 102500 and in ORPHANET under the reference ORPHA955. This disease mainly affects the connective tissue and belongs to the osteolysis syndromes group [1]. It is also known as acro-dento-osteo-dysplasia, acroosteolysis with osteoporosis and changes in the skull and mandible, arthro-dento-osteo-dysplasia and serpentine fibula–polycystic kidney syndrome. It is caused by a heterozygotic mutation of the gene NOTCH2 [2] located on chromosome 1p13-p11 and follows an autosomal-dominant inheritance pattern [3], although descriptions of cases with sporadic mutations can be found [4]. The prevalence of this disease is less than one person in one million (<1/1,000,000).

N. Hajdu first described the disease in 1948 [5], and the description was completed at a later date by D. Cheney in 1965 [6]. Since then, approximately 100 cases have been reported in the scientific literature allowing for the identification of a series of general features, which are shared by all patients, such as a phenotypic variability, an age-dependent progression and the presence of generalized osteoporosis and acroosteolysis of distal phalanges as well as other clinical manifestations [7].

The phenotypic variability [8] is the consequence of the variability of the expression of NOTCH2; hence, patients diagnosed with this disease may present with clinical differences between them. Moreover, this disease presents a wide and specific clinical spectrum so it may be difficult to encounter in full in a single patient.

This disease has a degenerative nature [9]; therefore, the clinical manifestations worsen over time with the onset of many changes from early childhood to late adulthood.

The osteolysis of distal phalanges and generalized osteoporosis [10] found in all cases with HCS is accompanied by a series of clinical manifestations that, as we previously stated, may vary between patients.

These differences include cranial alterations [5] such as dolichocephaly, delayed suture closure, presence of multiple wormian bones, absent frontal sinuses, thickened dome of the skull, occipital prominence, bathrocephaly, elongated sella turcica and micrognathia, which may lead to complications such as basilar invagination [11]), hydrocephalus [12] and syringomyelia [13]; facial alterations such as hypertelorism, sinofridia, thick hair, low-set ears, elongated philtrum, small jaw, high-arched palate, premature denture loss [14], unusually deep voice and hirsutism; and musculoskeletal alterations such as kyphoscoliosis, short stature, fractures of long bones, acroosteolysis [15], progressive distal bone resorption, joint laxity, bone demineralization, and osteoporosis [16]. Other clinical manifestations may include delayed motor development, hearing loss, changes of the voice, congenital heart disease [17], alterations of the respiratory, renal and digestive systems, plantar ulcers and hernias. It must be highlighted that there is a subgroup of patients who present with serpentine fibula and polycystic kidneys [18,19].

The definitive diagnosis is reached by genetic sequencing [20], although the initial diagnosis is established based on the observation of external appearance and the radiological findings [21]. There are certain overlapping features with other diseases such as scleroderma, sarcoidosis, progeria, pycnodysostosis, Whyte-Hemingway, Winchester and Alagille syndrome, which, on occasions, may have to be included in the differential diagnosis.

Currently, there is no definitive or effective pharmacological treatment for HCS, although there are projects underway studying this aspect [22]. At present, the treatment for this disease is centered around the management of complications and underlying problems with the aim of improving the patient's quality of life and life expectancy.

There are currently more than 7000 rare diseases in the world, of which only 800 have minimal scientific knowledge. In general, rare diseases and in particular, Hajdu–Cheney syndrome, have a low prevalence and few registered cases. The study population sample is dispersed, with a variable phenotype, little-described clinical symptoms and different evolution.

Considering the basic characteristics of this disease, a field of study with many aspects to be explored, can be seen, highlighting aspects such as the complete definition of the phenotype and clinical symptoms through the study of existing cases.

2. Patient Information

The patient was a 54-year-old Caucasian woman (Figure 1). Her mother had no complications during pregnancy and none were present at birth. There was no family history of similar clinical manifestations and she was the youngest of four sisters. She had no children of her own.

The patient was diagnosed with congenital acroosteolysis or Hajdu–Cheney syndrome, osteoporosis, disabling coxarthrosis with acetabular protrusion, musculoskeletal alterations, flat feet, short stature, dysplastic facies, dorsal hyperkyphosis, vitamin D deficiency, low bone density in the trabecular bone, fibrocystic mastopathy, bilateral hearing loss, intermittent mild neutropenia, dysphonia with mild sleep apnea without oximetric repercussions, chronic gastritis and constipation, premature loss of teeth, and adjustment disorder with a longstanding depressive disorder.

The patient was born in 1967. The first clinical registry was obtained at the age of six years after a visit to the Nuestra Señora del Prado Hospital in Talavera de la Reina (Toledo, Spain). After clinical examination, the patient was found to have a moderate psychomotor delay, dysplastic facies, alterations of the extremities and delay in stature closure. The first diagnostic suspicion was pycnodysostosis.

Figure 1. Current photograph of the patient.

At the age of 9 years and 11 months, at a follow-up consultation, the following data were compiled from the physical examination: good nutritional state, stature 134 cm, weight 26 kg, presence of dysplastic facies, underdeveloped dentition, a systolic murmur identified at cardiac auscultation, pubic hair beginning to develop on the major labia and upper zone, observation of symmetric upper extremities with a proportionate shortening of the arm over the forearm during the examination of the musculoskeletal apparatus, prominence on the internal face of both elbows affecting pronation–supination movements, swelling of terminal phalanges of hands with watch-glass nails without local pain, and

examination of lower extremities found bilateral genus valgus with widening of the distal feet and toenails of the same characteristics as those of the hands (Figure 2).

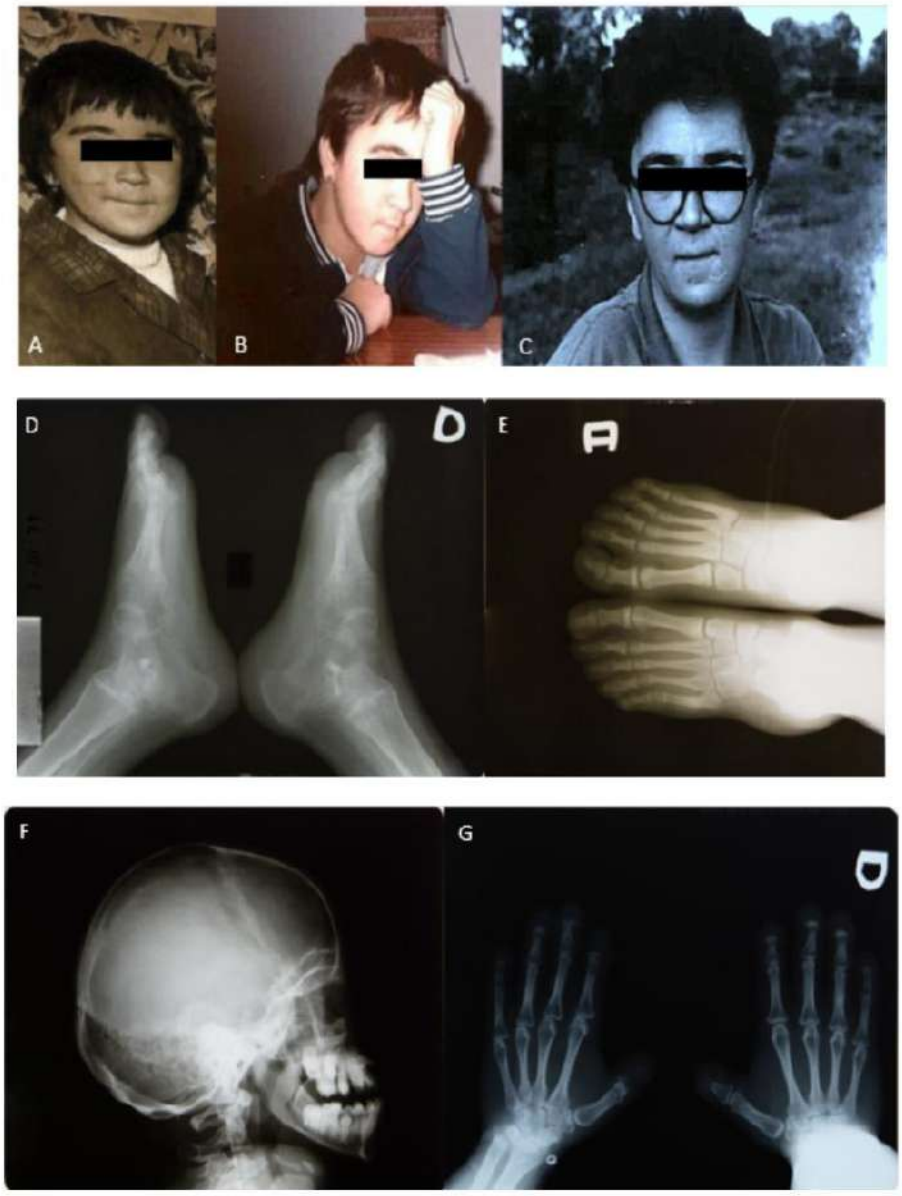

Figure 2. Childhood photographs. Radiologic controls 1977–79. (**A**–**C**) Portraits of childhood. (**D**) Lateral anteroposterior X-ray of the feet in 1977. (**E**) Frontal X-ray of the feet in 1977. (**F**) Lateral X-ray of the skull in 1978. (**G**) Frontal X-ray of the hands in 1979.

An X-ray of the skull showed dolichocephaly, elongated sella turcica and alterations of the sphenoid fissure. X-rays of the arms revealed bilateral dislocation of the radioulnar joint and acroosteolysis of the hands.

In 1977, the patient was diagnosed with idiopathic progressive acroosteolysis. The description of the case was performed by analyzing, in detail, the different clinical manifestations within their physiologic context and in a chronological order with the aim of evaluating the progressive nature of the syndrome.

3. Musculoskeletal Features

In 1978, the patient was referred to the traumatology service of the Nuestra Señora del Prado Hospital for the assessment of valgus flat foot that did not improve with orthopedic insoles. Finally, a surgical procedure was performed and the use of orthopedic footwear was recommended.

In 1987, due to the natural progression of the disease of her feet, the patient developed third degree pes cavus with irreducible claw toes and a marked equinus position of her left foot. She also presented with a persistence of recurvatum of the left knee and later developed the same problem on her right knee as well as bilateral genu valgum. Then, cephalic necrosis of the left hip appeared causing painful limitations with movements of the hip joint.

In 1993, the diagnosis worsened as the diseases progressed over time and deformities of the hands, feet, knees, hips and spine were present, accompanied by a considerable loss of strength (Figure 3).

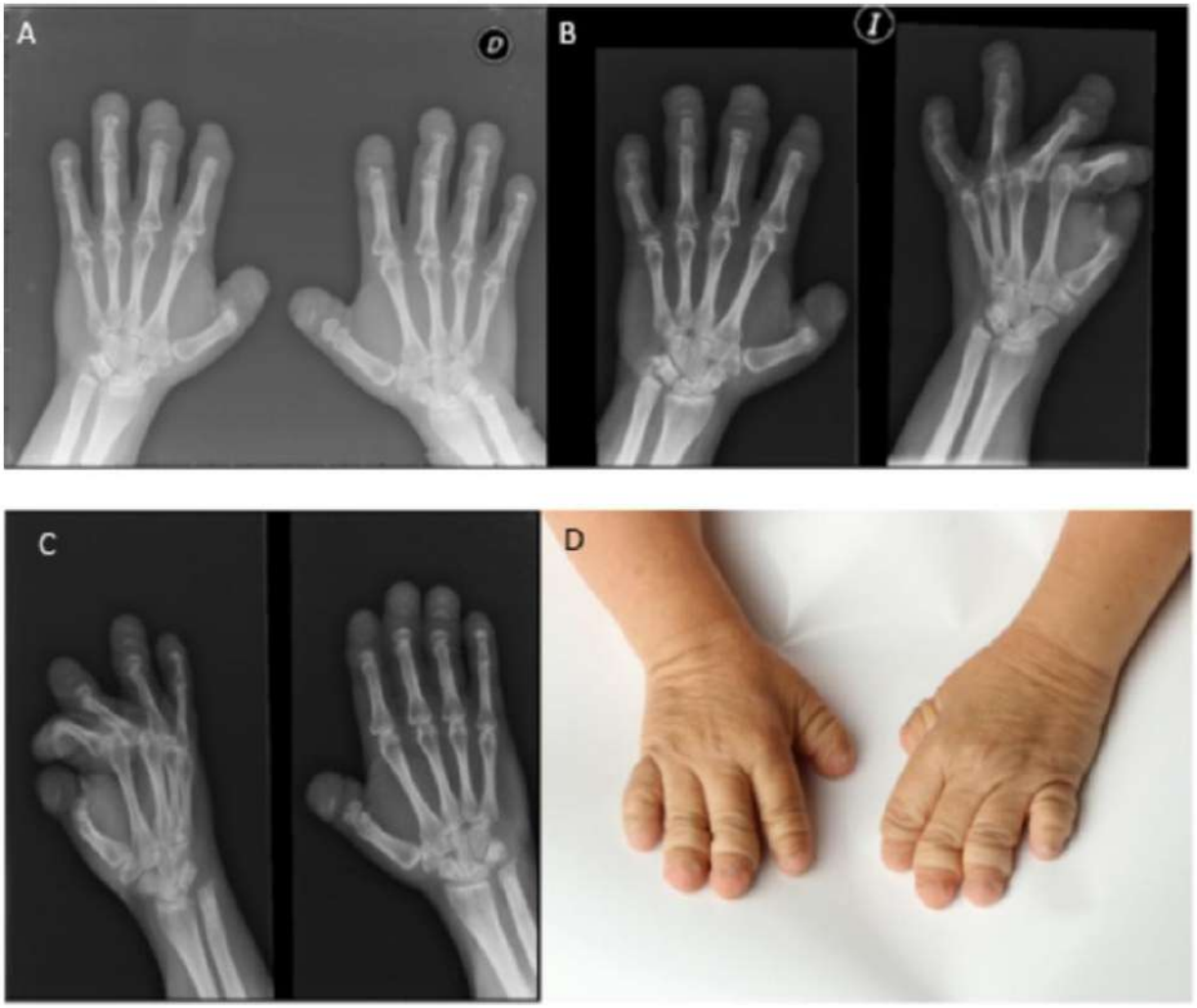

Figure 3. *Cont.*

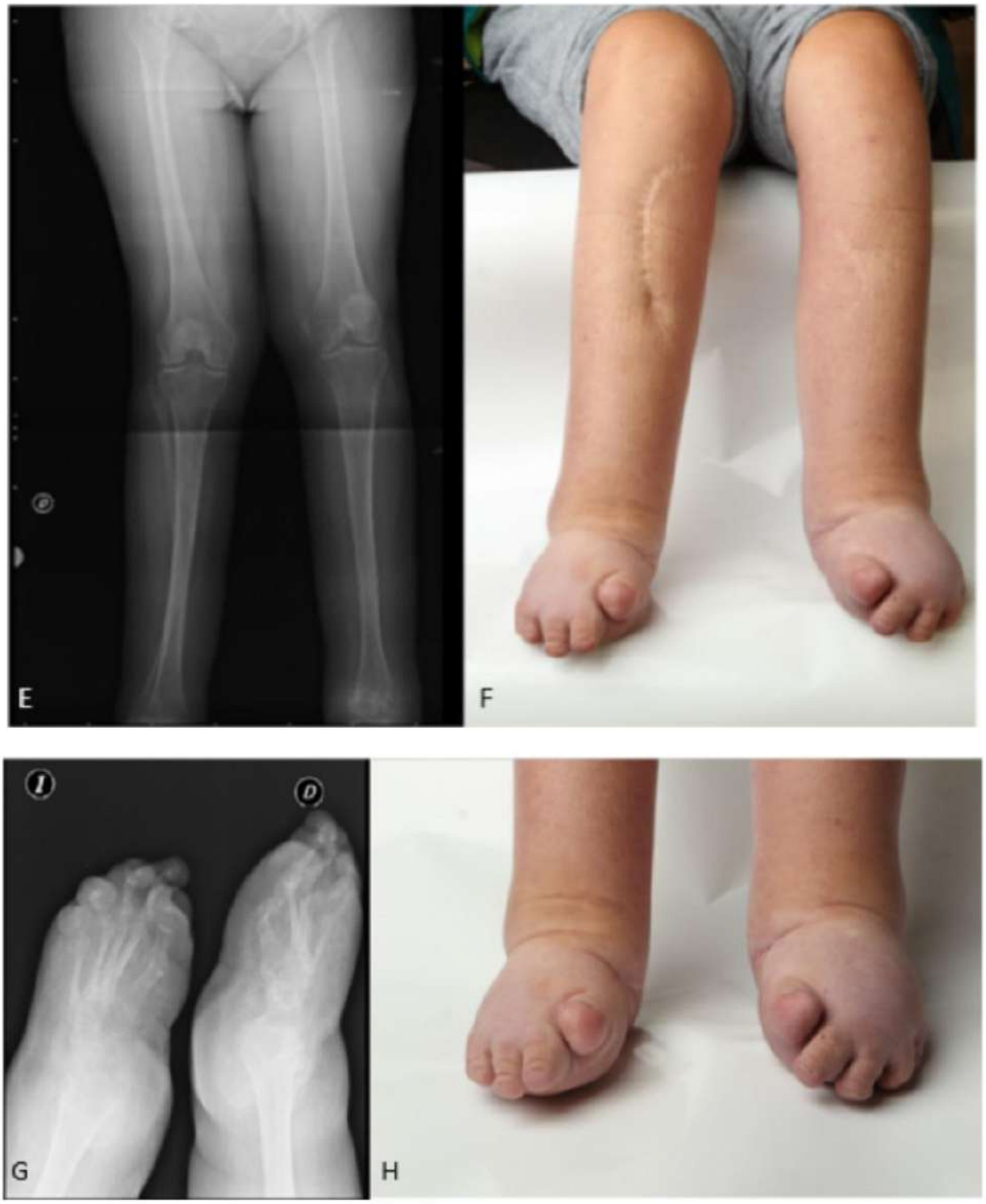

Figure 3. *Cont.*

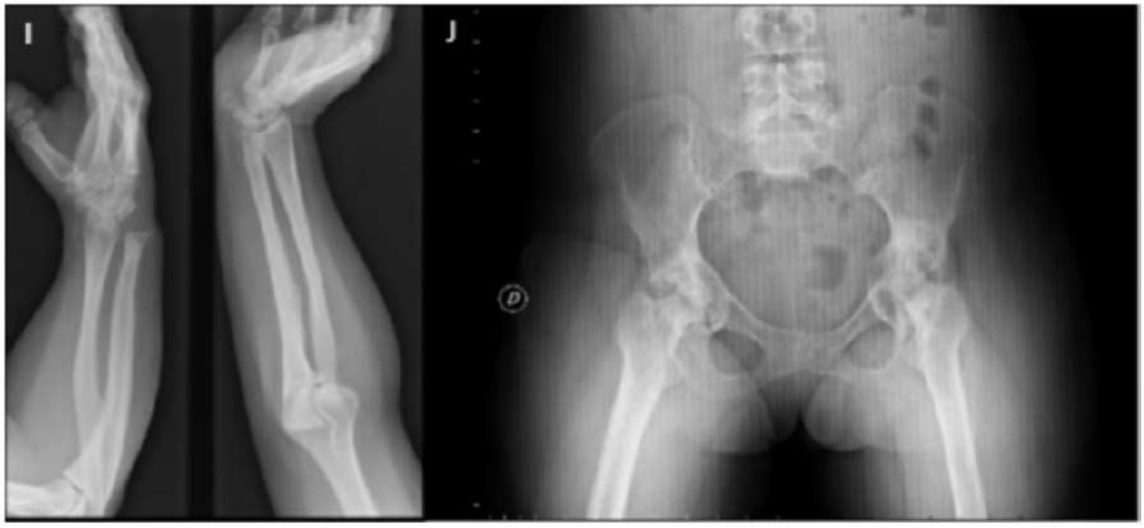

Figure 3. Radiologic controls. Phenotypic progression. (**A**) Radiological control hands in 2008. (**B**) Radiological control hands in 2011. (**C**) Radiological control hands in 2014. (**D**) Photography hands in 2021. (**E**) Serpentine fibula in 2002. (**F**) Photography legs in 2021. (**G**) Radiological control feet in 2014. (**H**) Photography feet in 2021. (I) Radiological control forearm in 2016. (J) Anteroposterior radiological control of the hip in 2013.

In 1996, the patient visited the 12 de Octubre Hospital. During these visits, alterations of facial bones and the jaw were identified, and many teeth were found to be missing alongside alterations at the point of implantation. Other findings include early onset of hip arthritis, a complete disappearance of the third and second phalanges of the first and second fingers of her left hand, severe deformities of both feet that, alongside her knee deformities and a lumbar hyperlordosis, practically impeded walking. The patient walked with difficulty using crutches, although she began to use a wheelchair for longer distances.

In 1998, the patient underwent a bone biopsy, the results of which showed findings consistent with osteoporosis.

In 1999, new severe lesions of the distal phalanges of both feet were registered and a progressive destruction of areas of the tarsus, metatarsus and toes with spontaneous anquilosis of the left ankle in equinus position was found. The patient also had other congenital alterations such as a posterior dislocation of the radius of both elbows with functional limitations and a spondylosis of L5 that was identified during imaging controls. Later evaluations found a worsening of mobility and positioning of both feet, including the ankles, as well as a progressive destruction of both hips and spontaneous pain and contracture in flexion and internal rotation of the left hip. At this stage, both feet had lost all anatomical structure. Due to the auto aggressive nature of the syndrome, the patient was considered for surgical intervention for the insertion of hip prosthesis.

In 2008, the patient was diagnosed with bilateral collapse of femoral heads.

By 2012, the patient was limited to a wheelchair due to a complete inability to walk. There was also a progressive bone decalcification due to the lack of deambulation, further deformities in both hands, a left acetabular protrusion and bilateral coxarthrosis.

In 2013, a pelvis CT was obtained, which found a marked deepening of the femoral heads within the acetabular and bilateral protrusion; a diagnosis of Otto pelvis was made. The patient required evaluation for hip replacement. Her clinical condition was poor, with considerable disability requiring continuous assistance for everyday activities and transition to a motorized wheelchair to enable mobility. The patient complained of pain in the feet and edemas and of the inability to remain in a standing position due to the extensive destructuration of her coxofemoral joints.

In 2016, the clinical condition of her pelvis required referral to the Ramón y Cajal Hospital for evaluation of a possible bilateral hip replacement arthroplasty. Whilst the ongoing evaluation, the patient suffered a motor vehicle accident that has had a significant impact on her condition, notably worsening her general condition and her prospects of recovering any deambulation.

The accident suffered in 2017 marks a before and after in the progression of her disease. The patient was run over by a vehicle, taking a fall to the ground, which caused multiple lesions, mainly to her legs.

After the accident, the patient was referred to the pain management unit due to a severe worsening of the pain in her hips, ankle and left foot, although no fractures were identified.

By 2018, there was a slight improvement of the pain and the department of rehabilitation carried out a new evaluation of the possible impacts of a hip replacement but resolved to not move forward with the arthroplasty, based on the premise that the patient was unlikely to regain the ability to walk unassisted despite the surgical intervention.

In 2019, scleroderma was identified in association with the already present acroosteolysis.

Over the years of follow-up, bone density studies were carried out every 2–3 years by the department of rheumatology to study the progression of the disease regarding osteoporosis in order to adapt the established pharmacological treatment. Bone densitometry of the spine and the hip were performed. Tables 1 and 2 show the data obtained in the latest studies.

Table 1. Evolution of the reviewed parameters of bone densitometries of the spine.

Date	Age	Dmo (g/cm^2)	Difference (%)	Difference/DE
10 October 2005	38	0.819		
7 May 2008	40.5	0.872	6.5	5.3
2 December 2011	44.1	0.914	11.6	9.5
29 May 2014	46.6	0.856	4.5	3.7
10 May 2016	48.5	0.814	−0.6	−0.5

Table 2. Evolution of the reviewed parametres of bone densitometries of the hip.

Date	Age	Dmo (g/cm^2)	Difference (%)	Difference/DE
10 October 2005	38	0.846		
2 December 2011	44.1	1.933	128.5	77.6
29 May 2014	46.6	1.508	78.3	47.3
10 May 2016	48.5	1.300	53.7	32.4
10 December 2018	51.1	1.035	22.3	13.5

In the densitometry control of 2012, there was an improvement in the parameters of bone density with regards to the 2005–2009 studies.

The last densitometry was performed in 2021. The results found that the bone density in the lumbar spine (L1–L4) was 0.673 gr/cm^2 and 0.885 gr/cm^2 in the left hip. Therefore, the diagnosis for the lumbar spine is compatible with osteoporosis and with osteopenia for the left hip.

4. Respiratory Features

In 2019, the patient was referred to the department of respiratory medicine for the study of dysphonia and a sensation of shortness of breath when speaking. It was decided to continue the study of her dyspnea in the sleep disorders' unit to rule out noctur-

nal hypoventilation. A respiratory polysomnography study was carried out to establish baseline conditions.

Results showed a saturation tracing with several dips constituting a desaturation index of 15.1 per hour or registry, with a time of saturation below 90% (TC90) of 0.4%, and initial saturation of 95%, minimum saturation registered 80% and a mean saturation of 93.4%.

The mean heart rate was 83.2 bpm, with a maximum of 119 bpm and a minimum of 69 bpm. Regarding the respiratory signal, there was a tracing with apneas and hypopneas accompanied with oxygen desaturation that constituted an apnea–hypopnea index (AHI) of 15.9 events per hour of registry (changing from 5.1% of the registry in supine position, with a AHI of 19.6 and CT90.0%), with an index of central apneas of 0.3 per hour of registry, an index of obstructive apneas of 2.1 per hour or registry, an index of mixed apneas of 0 per hour of registry and an index of hypopneas of 13.5 per hour of registry. These results determine the existence of a mild to moderate sleep apnea–hypopnea syndrome without oximetric repercussions.

5. Ear, Nose and Throat Features

The patient has been followed-up with since 2019 for dysphonia and hypoacusia. During the physical exam, a small hyperemic polyp was identified on the anterior third of the right vocal cord. The patient was found to have a narrow nasal valve and a deep voice. An audiogram was performed, which detected signs of hypoacusia (Figure 4).

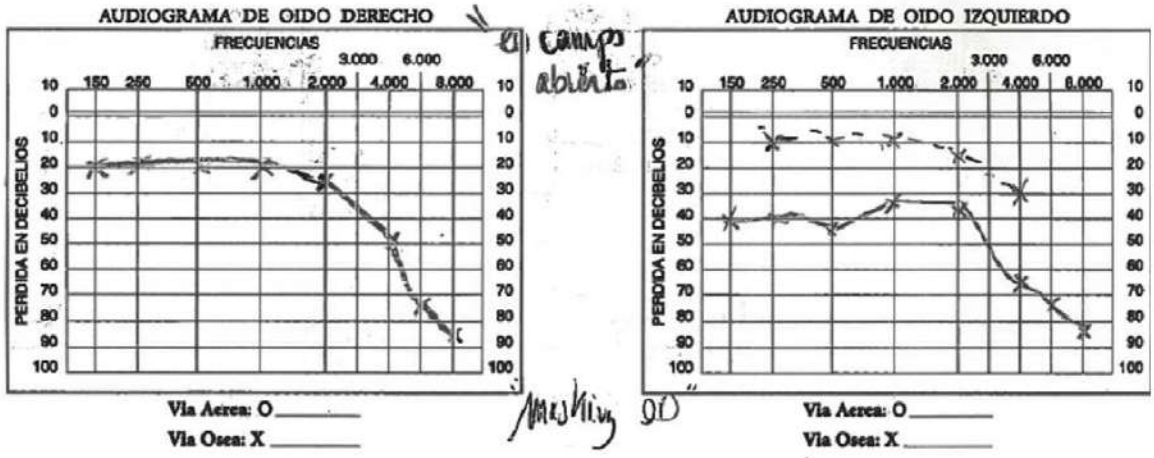

Figure 4. Audiogram of patient.

6. Gastroenterology Aspects

In 2011, an upper endoscopy identified signs of gastritis and a peptic-like lower esophageal ring.

In 2018, the patient was referred to the department of gastroenterology for the study of her dyspepsia. The patient complained of a longstanding intermittent diffuse abdominal discomfort and chronic constipation. Several lab and imaging studies did not identify any findings of interest.

7. Gynecology Aspects

The patient has been followed by the department of gynecology since 1994 for discomfort in both breasts.

In 1994, a bilateral mammogram report described very dense breasts with a predominant fibroglandular component compared to fatty tissue. Several cysts were seen in both

breasts, the largest in the right breast of 18 × 14 mm. The patient was diagnosed as having bilateral fibrocystic mastopathy.

In 2001, a new bilateral mammogram detected several 2 cm nodules in the left breast, disperse bilateral calcifications that were more evident in the left breast in relation to sclerotic adenosis. A fine needle aspiration of the left breast allows for the pathology diagnosis of fibroadenoma.

In 2003, several cysts that resemble fibroadenomas were detected in both breasts.

In 2006, several new benign nodules were detected. Biopsies of both breasts were obtained, and the results confirmed the diagnosis of fibrocystic mastopathy.

In 2007, multiple bilateral cysts were observed, some with echogenic contents that gave them a solid aspect. A biopsy was taken for confirmation. The biopsy report stated duct ectasia and fibrocystic mastopathy.

In 2011, multiple simple cysts were found in both breasts, some of them with a less characteristic liquid content, that were most likely fibromas.

In 2016, a 2 cm well-defined solid nodule was found in the inferior quadrant of the left breast. The decision was made to carry out an ultrasound-guided core needle biopsy. The diagnosis was fibroadenoma.

8. Maxilofacial Features

In 2011, the patient herself sought treatment as she had a complete loss of teeth and an extreme maxillary atrophy. She requested surgical intervention for the implant of teeth. However, an orthopantomography confirmed the high degree of atrophy, describing very fine alveolar edges and type IV maxillomandibular atrophy. Due to the state of the jaw bones, the surgical intervention was not considered (Figure 5).

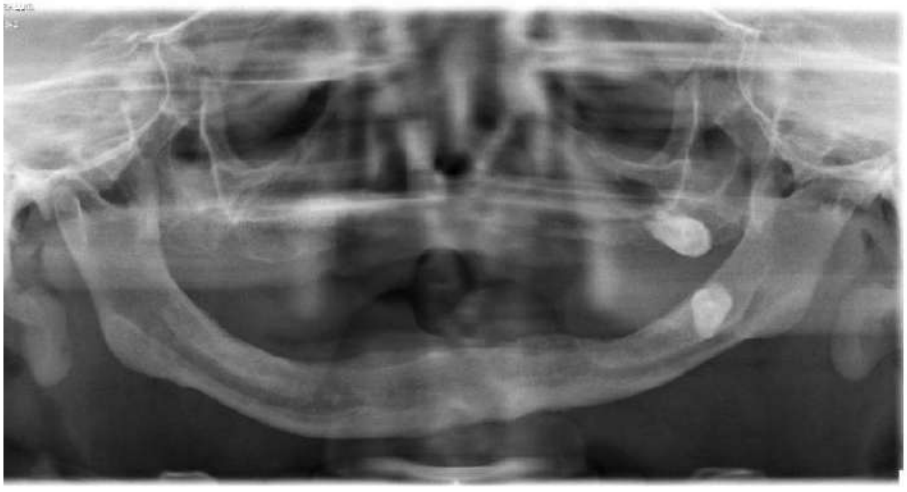

Figure 5. Orthopantomography of patient.

9. Hematology Aspects

In 2018, during a routine lab analysis, a neutropenia of 900 was detected, leading to referral to the department of hematology. The patient did not have a history of fever or recurrent infections.

She was diagnosed with a mild–moderate intermittent cyclic neutropenia of an unknown etiology, although this was possibly idiopathic, autoimmune or drug-induced.

10. Psychiatric Aspects

After the accident that took place in 2017, the patient required evaluation by the psychiatric team. She suffered from anxiety that negatively impacted her daily life. Her extreme dependency on other people for all activities made her feel sad and the appearance

of nightmares about the accident caused her sleep disturbances. She described feelings of apathy regarding the impossibility of recovering her former life. The patient required medication in order to sleep and expressed difficulties for paying attention and concentrating and a certain hopelessness about her current situation. She presented no sensory perceptual alterations, and her judgement of reality was preserved.

The patient was diagnosed with a prolonged adjustment disorder with clinical manifestations of depression and anxiety secondary to the pain and loss of autonomy after her traffic accident.

11. Psychosocial Aspects and Lifestyle

The patient experienced significant changes in her lifestyle and the psychosocial spheres of her life after the 2007 accident. The functional limitations of her lower extremities did not allow her to carry out everyday activities independently or with any degree of autonomy. Activities such as bathing, cooking, getting dressed, and driving were activities she once carried out daily but were no longer possible. She could not drive and wore nighttime diapers to avoid unnecessary painful bathroom visits. She used a transportation crane for most of her mobilization. The levels of depression and anxiety that arose from these situations were high.

To evaluate the degree of depression, we used the Patient Health Questionnaire (PHQ-9) [23], obtaining a score of 18/29, which indicated a moderate to severe level of depression requiring pharmacological and interventional treatment. The level of anxiety was assessed using the General Anxiety Disorder scale (GAD-7) [24], where she scored 21/21, indicating severe symptoms of anxiety. We also used the Health Questionnaire SF-36 [25] to assess her quality of life, obtaining scores of 24 in the section of physical health and 25 in the section of mental health. Both scores below 30 confirmed a subpar quality of life.

12. Milestones

Table 3 shows the main milestones in the description of the case.

Table 3. Main milestones in the description of the case.

Important Milestones	Year
Birth	1967
First medical registry	1973
Diagnostic suspicion	1973
Definitive diagnosis	1977
Pes valgus surgery	1978
Walks using crutches	1996
Diagnosis of breast fibroadenomas	2001
Begins treatment with bisphosphonates	2006
Wheelchair	2012
Ends treatment with bisphosphonates	2012
Evaluation for possible hip replacement	2016
Traffic accident	2017
Dependency for activities of daily living	2017
Diagnosis of prolonged adjustment disorder with clinical manifestations of depression and anxiety secondary to the pain and loss of autonomy after accident	2017
Diagnosis of neutropenia	2018
Diagnosis of OSAHS	2019
Scleroderma related to HCS	2019

13. Diagnosis Related Problems, Differential Diagnosis and Prognosis

When it comes to rare diseases, one of the main problems that often arises is the late diagnosis. Approximately 80% of rare diseases have a genetic origin, thus, most of the time, the definitive diagnosis is only obtained after genetic sequencing. A prior diagnostic

suspicion and a careful consideration of the observed clinical findings are essential. In the case of this specific disease, there is a useful clinical tool that was designed by Brennam et al. [9] that established inclusion criteria based on physiological parameters and genetic inheritance. The complexities in the diagnosis of Hajdu–Cheney syndrome arise when there are clinical findings that are also present in other diseases, leading to several crossover points that increase the possibilities and the need for a differential diagnosis. Specifically, in the case we have presented, the first diagnostic suspicion that arises is pycnodysostosis.

Pycnodysostosis [26] is also a rare disease that is caused by mutations in the gene that codes cathepsin K (located on 1q21). The most frequent clinical manifestations include osteosclerosis, short stature, acroosteolysis of the distal phalanges, bone fragility, dysplasia of the clavicula, cranial malformations such as a large skull, wormian bones and persistence of the anterior fontanelle and a small jaw. Dental anomalies as well as irregular and brittle nails are often seen. The disease is not progressive.

As one can see, there are clinical links between the two syndromes, which complicates making the diagnosis. The study of the complete phenotype of the disease, the observation of the clinical findings and, finally, genetic sequencing, are the key elements needed to arrive at the definitive diagnosis.

The prognosis of patients affected by HCS depends on the severity of the disease, clinical complications and the degenerative progression of each patient. The generalized osteoporosis and the development of acroosteolysis will likely cause fractures, limit deambulation and lead to dependency for basic everyday activities. The most frequent complications in this disease include basilar invagination, which causes neurological alterations, or chest wall deformities that give way to ventilation restriction.

14. Therapeutic Interventions

Table 4 shows the therapeutic interventions to which the patient has been subjected.

Table 4. Therapeutic interventions.

PHARMACOLOGICAL	
PAINKILLERS	
DICLOFENAC 50 mg every 12 h	Treatment for pain management is established following the recommendations of the World Health Organization (WHO) in their analgesic ladder. The strategy consists of a series of drugs administered regularly and rescue medications for the occasions when routine treatment is insufficient for pain control.
PARACETAMOL 650 mg every 4 h	
TRAMADOL HYDROCHLORIDE 50 mg every 6 h (rescue medication)	
DAFALGAN (paracetamol) 1 gr every 6 h (rescue medication)	
METAMIZOLE 575 mg every 6 h	
FENTANYL patch 12 mcg every 72 h	
TRAMADOL HYDROCHLORIDE 200 mg at breakfast	
CELECOXIB 200 mg every 24 h	
SUPPLEMENTS	
OSSOPAN® 400 mg every 24 h	Supplements of calcium and vitamin D are administered together to boost their effect against osteoporosis.
SUPRADYN® PROTOVIT 9 drops every 24 h	
ORAL CALCIUM 1 gr every 24 h	
VITAMIN D3 8000 U every 24 h	
IDEOS® 500 mg every 12 h	
HIDROFEROL® 0.266 mg every 15 days	

Table 4. *Cont.*

PHARMACOLOGICAL	
ANTI-ACIDS	
OMEPRAZOLE 20 mg every 24 h	Due to the diagnosis of gastritis and the polypharmacy the patient receives, an antiacid is required to protect her stomach lining.
BISPHOSPHONATES	
ACREL® 35 mg weekly (risedronic acid)	The treatment with bisphosphonates began in 2006 and was cut off in 2017 after an improvement in densitometric parameters.
ADROVANCE 70 mg weekly (alendronic acid/colecalciferol)	
ANTIDEPRESSANTS	
XERISTAR® 60 mg every 12 h (duloxetine)	Antidepressant treatment begins in 2017 after the diagnosis of a prolonged adjustment disorder with clinical manifestations of depression and anxiety secondary to the pain and loss of autonomy after her traffic accident.
DEPRAX® 100 mg every 24 h in the evening (sertraline)	
DIAZEPAM 5 mg every 12 h	
STILNOX® 10 mg every 24 h in the evening (zolpidem tartrate)	
VENLAFAXINE 37.5 mg every 24 h	
ZARELIS® 75 every 24 h	
LAXATIVE	
MOVENTING® 25 mg at breakfast (Naloxegol)	The treatment of chronic constipation requires the regular use of laxatives.
SURGICAL	
Pes planus valgus	Surgical intervention in 1978 of the patient's pes planus valgus determines the use of orthopedic insoles and footwear.
Surgical lumpectomy of a benign breast lesion	In the context of a fibrocystic mastopathy with fibroadenomas, surgical intervention is required for the correct evaluation of a breast lump.
SELF-CARE	
Daily basic walk Avoid overweight Maintain physical activity Intellectual activity	Self-care recommendations are designed to maintain as much physical and intellectual activity as possible and to avoid overweight as a preventative method against disease progression.

15. Discussion

The case we have described presents the three main features of Hajdu–Cheney syndrome.

The phenotypic variability [8,27,28], a consequence of the variability of expression of NOTCH2, is evident when comparing this case to other cases diagnosed with HCS that have been published in the scientific literature. Cases such as those presented by Swan et al. [29], Ades et al. [12] and Takatani et al. [30] all show differences in their physical appearance and clinical presentation despite having the same diagnosis.

The degenerative nature [31] is evident in most of the radiological findings that we analyzed and in the continuous deterioration of the patient's autonomy. This fact was also described by Harnasch [32] in the description of their case, which reports that the patient began to suffer a gradual loss of strength until becoming completely dependent for everyday activities.

Similar cases of the acroosteolysis of the distal phalanges and the generalized osteoporosis that this patient presented are described in the majority of cases diagnosed with HCS that are published to date. The cases reported by Rosenmann et al. [33], Elias et al. [34] and Bruckner et al. [35] suggest that the most prevalent signs of HCS are acroosteolysis and generalized osteoporosis.

Diagnostic reasoning is guided by observation and the radiological findings [21]. Brennam et al. [9] created a clinical tool to facilitate the diagnosis of this syndrome. The tool includes a list of physiological parameters and genetic inheritance as inclusion criteria for HCS. Among the included features are acroosteolysis, premature loss of teeth, short stature and dysplastic facies. The case we present in this paper presents all the above mentioned features, and therefore, complies with the inclusion criteria and positively guides the case towards the diagnosis of HCS.

During the first medical visits, the suspected possible diagnosis was pycnodysostosis [26] due to the phenotypic similarities that were found. A similar debate occurred in the case reported by Herrmann et al. [36].

Once a suspected diagnosis is established, the definitive diagnostic confirmation must be determined by Gibofsky genetic sequencing [20]. In this case, a constitutional cytogenetic study in peripheral blood was performed in 1998. The results after the analysis of 15 metaphases showed a karyotype without numeric or structural anomalies. In 2020, considering the lack of further genetic studies, the patient was referred to the genetics department for complete genetic sequencing.

Hajdu–Cheney syndrome generally follows an autosomal-dominant inheritance pattern, as reported by Majewski et al. [3]; however, sporadic cases do exist, such as the case presented by Descartes et al. [4].

Over the course of the follow-up of this patient, a series of findings comparable to previously described cases of this disease have reinforced the available knowledge on this disorder. At the same time, new aspects arise that may serve as a guide for future lines of research.

The musculoskeletal alterations that are presented in this case, such as the generalized osteoporosis and the acroosteolysis of the distal phalanges, are two of the main manifestations of this syndrome that are also present in the majority of cases that have been studied, as Letchumanan et al. [15], Stathopoulos et al. [16] and Nunziata et al. [37] report in their publications.

Siklar et al. [38] described the link between growth hormone and short stature in patients with HCS, a noticeable aspect in this case. Characteristics of a dysplastic facies at a cranial level, including dolichocephaly, elongated sella turcica and alterations of the sphenoidal fissure, are present in cases such as the case Hajdu et al. [5] described in their first description of the syndrome, in a patient with cranial alterations.

The bilateral genu valgum that our patient presented has previously been described in different occasions by Willians [39] and Weleber et al. [40].

A frequent finding in Hajdu–Cheney syndrome is watch-glass nails, an element which is present in this case and that has also been described in the literature by Rosenmann et al. [33], among others. They present a patient with a particular finding that is also seen in this case: the implication of the radial head.

The disease progresses over time, a fact which is most noticeable in the deterioration of the musculoskeletal apparatus. This patient presented deformities of the hands, such as those described by Jiménez et al. [41] Shurtleff et al. [42] Brown et al. [10] and Ventosa et al. [43]; of the feet, such as those described by Greenberg et al. [44] and Colmenares Roldán et al. [45]; of the knees, as discussed by Weleber et al. [40]; and of the spine, reported by Vissarionow et al. [46] and Chawla [47]. This worsening at a skeletal level is accompanied by a considerable loss of strength that increases the disabling nature of the syndrome.

The presence of hyperlordosis and hyperkyphosis in this case made walking progressively difficult. Initially, the patient was able to manage with the help of crutches, but this became no longer possible and she progressed to requiring a wheelchair for any kind of mobilization. In the case described by Rosenmann et al. [33], the same clinical findings were present.

The disabling coxarthrosis with acetabular protrusion is another sign of the degenerative nature of the disease as it can be seen how it is worsening as time passes. Otto pelvis

In this case, there is a clear before and after in the progression of the disease related to the traffic accident the patient suffered in 2017. The patient was run over by a vehicle, causing her to fall and suffer multiple lesions. This event had a noticeable negative effect on her day to day life, leaving her completely disabled for most daily activities, increasing her level of dependency and further developing mental disorders such as stress, anxiety and depression.

At this point, it is important to note that there are studies that justify the psychological burden and the increase in mental disorders that occur in patients with rare diseases [58].

With regard to treatment, several aspects can be analyzed: pharmacological, surgical and self-care.

The studies on pharmacological treatments for this syndrome do not present clear evidence on their efficacy. Relevant studies on pharmacological treatments for HCS include that by Sakka et al. [59], who worked on a therapy that uses bisphosphonates and found oscillations in bone mineral density indexes of the lumbar spine. At the beginning of the study, the values decreased, then increased in response to treatment, but the effect did not persist after its interruption. Pittaway et al. [22] also studied bisphosphonates but obtained different results for each patient that were dependent on age. Adami et al. [60] tried obtaining an increase in bone mineral density with denosumab but acroosteolysis persisted. Tsinopoulou et al. [61] and Al-Mayouf et al. [62] experimented with pamidronate, without achieving a curative result. Hwang et al. [63] tried to slow down the process of bone degradation using zoledronic acid, and in 2007 and 2008, McKiernan et al. [64,65] carried out a pharmacological study to treat osteoporosis in HCS with an antiresorption and anabolic therapy. Treatment with bisphosphonates has a negative impact on the development of surgical interventions at the oral level because they hinder healing and increase the risk of osteonecrosis of the jaw [66].

The surgical intervention of flat feet that was performed in 1978 is part of the different surgeries that are mentioned in this case. Studies on surgical interventions in HCS are those by Mattei et al. [67] on cervical kyphotic deformities in patients with osteoporosis and by Murtagh-Schaffer et al. [68] on spinal reconstruction. In this case, bilateral arthroplasty hip replacement was a treatment option that was considered but that was finally not pursued for clinical reasons. The papers by Yamaguchi et al. [69] and August et al. [70] on the specific indications for the treatment of patients with HCS before surgery must also be mentioned.

Current treatment for HCS is mainly centered on the management of the complications that arise and on the treatment of the underlying problems in order to improve the patient's quality of life and life expectancy. In this case, several self-care recommendations were made, including maintaining an active as possible lifestyle, both physically and intellectually, and avoiding overweight as a preventative method against disease progression.

16. Limitations

The limitations we have identified in the development of this case study are directly related to the low specificity of the clinical studies that were performed. The lack of a general perspective on the progressive nature of the disease and a lack of awareness with regard to the disease itself have a negative impact on the follow-up of the case.

It would be of scientific interest to perform a genetic study in order to identify the exact underlying mutation and relate it to the phenotype. Confirming whether or not the patient has polycystic kidneys would provide vital information for follow-up. Regarding diagnostic testing, an updated complete radiological control to assess the possibility of basilar invagination, a typical complication in this syndrome, is recommended. Another frequent complication is ventilation restriction due to thoracic deformities, so this should also be considered. At present, the patient complains of a severe pain in the occipital area that does not resolve with her usual treatment. She also states that she experiences excessive tiredness with minimal efforts. Both signs are compatible with the most frequent complications of this syndrome, as have been previously mentioned.

17. Conclusions

The study of this case, in the context of general knowledge on Hajdu–Cheney syndrome, reinforces and justifies its three main features: phenotypic variability, age-dependent progression and acroosteolysis of the distal phalanges and generalized osteoporosis, all elements considered obligatory inclusion criteria for the diagnosis of this disease.

However, a complete and updated description of the phenotype of this syndrome, which includes a large sample of cases, is still needed.

The study of the hematological effects of HCS may constitute a possible future line of research of this syndrome.

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Abbreviations

HCS	Hajdu-Cheney syndrome
CT	Computed tomography
VAS	Visual Analog Scale
AHI	Apnea–hypopnea index
BPM	Beats per minute
FEV	Forced expiratory volume
FVC	Forced vital capacity
IT	Inspiration time
PHQ-9	Patient Health Questionnaire
GAD-7	General Anxiety Disorder scale
OSAHS	Oximetric sleep apnea–hypopnea syndrome

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CAPÍTULO IV

El segundo caso descrito, referente a un paciente pediátrico, fue redactado y posteriormente publicado con el título:

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Case Report

Hajdu-Cheney Syndrome: A Novel NOTCH2 Mutation in a Spanish Child in Treatment with Vibrotherapy: A Case Report

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Abstract: A case report of an 11-year-old boy with a de novo variant in NOTCH2 and clinical features characteristic of Hajdu-Cheney syndrome is reported, with acroosteolysis of the distal phalanges of the feet and hands, generalized osteoporosis, musculoskeletal and craniofacial alterations, short stature, bowing of long bones, vertebral anomalies, genu recurvatum, hypertrichosis, joint and skin hyperlaxity, atopic dermatitis, megalocorneas, micrognathia and frequent respiratory infections, among others. Treatment is with bisphosphonates in the framework of bone density improvement and with focal vibration therapy for rehabilitation of the musculoskeletal system and gait improvement. The three generalities of this pathology—phenotypic variability, degenerative character and the presence of generalized osteoporosis and acroosteolysis of the distal phalanges—are seen in this case, whose diagnostic confirmation was made by genetic study.

Keywords: Hajdu-Cheney syndrome; rare diseases; acroosteolysis; osteoporosis; bone resorption; NOTCH2

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1. Introduction

Hajdu-Cheney Syndrome (HCS) is classified as a rare disease, which like 80% of this type of pathologies is of genetic origin [1]. It responds to other names, such as Acro-dento-osteo-dysplasia; acroosteolysis with osteoporosis and changes in the skull and jaw; arthodentroosteodysplasia; and serpentine fibula syndrome and polycystic kidneys. It is referenced as ORPHA955 in ORPHANET [2] and #102500 in the OMIM database [3]. This syndrome mainly affects connective tissue and belongs to the group of acroosteolytic syndromes [4].

The prevalence of this disease is less than one person in one million (<1/1,000,000) [5] and is caused by a heterozygous mutation in the NOTCH2 gene [6], specifically on chromosome 1p13–p11. Although sporadic cases are observed [7], the pattern of inheritance is autosomally dominant [8].

Approximately 100 cases have been described in the scientific literature since the first description of the disease by N. Hajdu in 1948 [9]. Later, in 1965, D. Cheney completed the description with his study [10]. In all the cases described, the same general characteristics are observed: the degenerative character [11], phenotypic variability [12] and a picture of osteolysis of the distal phalanges and generalized osteoporosis [13], accompanied by other clinical manifestations.

The worsening of the disease over time increases the levels of dependence and disability in these types of patients [1].

The variability of expression of the mutated gene gives rise to different phenotypes for the same syndrome, so it is difficult to find all the clinical manifestations in the same person [11].

The osteolysis of the distal phalanges [14] and generalized osteoporosis seen in all patients diagnosed with this disease [13] are accompanied by a series of clinical manifestations.

The clinical spectrum is very broad, ranging from cranial alterations [9] such as the presence of Wormian bones, prominent occipital crest, dolichocephaly, batrocephaly and absence of frontal sinuses, among others. Coarse facial features such as hypertelorism, synofridism, low-set ears, arched palate, loss of teeth [15] and deep voice, among others, stand out. At the skeletal level, kyphosis and scoliosis, joint hyperlaxity and short stature are seen [16]. This syndrome affects the respiratory system with frequent infections, as well as the digestive system and the renal system [17]. Congenital heart disease [18] is another common manifestation of the pathology. Motor development, speech and hearing are also compromised. Inguinal and abdominal hernias, as well as plantar ulcers, are peculiarities of the syndrome. The association of polycystic kidneys and serpentine fibula is characteristic of this disease [19]. The most frequent complications are basilar invagination [20,21] and ventilatory restriction due to rib cage malformation.

The diagnostic orientation is made by observation of the phenotype and radiological controls [22]; it is true that there are clinical links with other diseases with which a differential diagnosis should be approached. These diseases with which a differential diagnosis should sometimes be made are Scleroderma, Progeria and Alaguille syndrome, among others [23]. In any case, the definitive diagnosis should be by genetic study [24].

Current treatment for this disease is aimed at addressing the clinical complications and correcting the problems that appear as the pathology evolves, highlighting all types of care aimed at maintaining and improving the quality of life of these patients [25]. At present, despite scientific advances on the subject, there is no effective or curative treatment for this rare disease [26].

2. Patient Information

The patient is an 11-year-old male of Caucasian origin. He is a student and properly vaccinated. He was born from a controlled pregnancy and normal delivery. He is the son of healthy parents and the youngest of three siblings. There is no family history of the same pathology. His brother of 21 years old has been operated on for cholesteatomas. His brother of 27 years old was diagnosed with spastic paraparesis due to a sporadic mutation of SPG4.

Genetically diagnosed with Hajdu-Cheney syndrome, he presents acroosteolysis of distal phalanges of feet and hands, generalized osteoporosis, cranial malformations, presence of Wormian bones, coarse facial features, short stature, joint hyperlaxity, recurrent respiratory infections and musculoskeletal alterations. The following picture (Figure 1) is a current photo of the patient.

The child was born in April 2011; pregnancy and delivery were normal, despite the diagnosis of gestational diabetes that was treated with insulin, without incident. Newborn weight was 4340 g, height was 54 cm and head circumference was 36 cm.

The mother was 44 years old, with a height of 171.3 cm, with menarche at the age of 15 years. She had two spontaneous abortions during her fertile life. The father was 45 years old and 173.8 cm tall. Both are without relevant pathologies. Maternal grandparents are second cousins. The family genogram can be found in Figure S1 of the Supplementary Material.

No anomalies were observed at birth. In the development of the first months of life, some hypotonia in the lower extremities and a resting posture of the neck in flexion were observed. Based on aspects such as these, in addition to the family history related to genetic diseases, it was decided to request a medical opinion on the patient's health status.

The first clinical record of the case already showed a delay in the closure of the posterior fontanel, which still persists, and a delay in dentition and language. He started walking at 9 months of age. Short distal phalanges, ribs with keeled deformity and Wormian bones in lambdoid suture were identified. At the cardiac and auditory level, no incidences were detected in the first few months. There was good growth, weight and height.

Figure 1. Current photograph of the patient.

Based on the clinical manifestations presented by the patient, an in-depth study was carried out by different medical specialties to identify a diagnosis that justified the phenotype and the clinical manifestations.

The following physical examinations and evaluations reflect the rapid evolution of the syndrome, and the findings found in conjunction with the clinical presentation meet a typical description of Hajdu-Cheney Syndrome.

Osteolysis was seen in the distal phalanges of the hands and feet with deformity, highlighting the shortening of the fourth and fifth metacarpals. Cranial palpation with slight occipital prominence at the level of the parietal suture, retromicrognatia and prominent sternum were seen. Other aspects to highlight in the first explorations were the diastasis of the supraumbilical rectum, tubiform thorax and pectus carinatum; genu recurvatum and valgus flatfoot; joint hyperlaxity and generalized cutaneous hyperlaxity, more noticeable in the elbow; mild hypotonia, but limiting in the day-to-day; delay and alterations in the order of dentition; atopic dermatitis, slight hypertrichosis, hard and dry hair, as well as abnormally populated eyebrows. Features such as ogival palate, full and slightly drooping cheeks and wide philtrum stand out. Ocular proptosis was observed with blue and megalocorneal sclerae. Colds and respiratory infections, such as pneumonia, were frequent. Cardiopulmonary study and neurological evaluation were normal, as was psychomotor development. At 2 years and 6 months, the weight was 12 kg, height 89.7 cm and head circumference 50 cm. The diagnosis was based on clinical observation, the study of the phenotype presented and the radiological findings. In May 2013, a genetic study was performed to confirm the origin of the pathology.

The genetic test performed was the sequencing of exon 34 of the NOTCH2 gene, by means of a blood extraction.

The procedure consists of the extraction of genomic DNA from the sample; PCR (polymerase chain reaction) amplification of the coding region, as well as the flanking intronic regions of exon 34 of the NOTCH2 gene was performed. DNA sequencing and capillary electrophoresis reactions were prepared. Bioinformatic analysis of the sequences was obtained by comparison with the reference sequence NG_008163.1.

A molecular study was performed for the analysis of small deletions/insertions and point mutations in the coding region and splicing sites of exon 34 of the NOTCH2 gene.

By direct analysis of the NOTCH2 gene, a heterozygous 18-nucleotide deletion (c.6446_6463del) was detected in the sample. This deletion presumably causes a change in the reading pattern and the appearance of a premature stop codon (p.Ser2149) at the protein level.

Once diagnosed, the clinical follow-up was performed in a multidisciplinary manner between the different medical specialties that best adapt to the needs and problems that arise during the development of the disease. The description of the case will be made by analyzing in detail the different clinical manifestations framed within its functional space. The following image, (Figure 2) are photos of the patient's childhood.

Figure 2. Childhood photos. (**A**) Newborn. (**B**) Facial features, 4 years old. (**C**) Full body, 4 years.

3. Musculoskeletal Features

There are several musculoskeletal disorders. In the first evaluations, complete radiological controls were carried out and repeated over time for identification and follow-up. In these diagnostic tests, different characteristic findings of the disease were observed, such as wide sutures with multiple Wormian bones and elongated sella turcica, at the cranial level; osteolysis of the distal phalanges of hands and feet, retraction of the distal metaphysis of the radius, widened distal metaphysis of tibia and fibula and of coarse aspects; hip dysmetries, scoliosis, flattening of D6 and biconcave vertebrae.

Peculiar facial features were also observed, with a mildly keeled thorax with tendency for lumbar kyphosis and scoliosis with the lower hip, with the axial axis slightly lateralized to the right. Thick hands with short distal phalanges and flexible flat feet of 4°, the left one bigger. Telemetry showed a right scoliotic attitude with a 5 mm hip descent.

Gait control was performed, and although it was correct and allowed him to jump and run, the use of corrective insoles was proposed.

The last radiological findings identified were a fracture of the fifth metatarsal in 2016 and a vertebral fracture in 2021.

In 2017, cervical protrusion was detected, which becomes more evident when coughing; after that, cervical ultrasound detected pulmonary herniation.

Magnetic resonance imaging was performed without finding signs of basilar invagination for the moment. A decrease in the height of the vertebral bodies of T7, T4 and T2 with vertebral biconcave morphology in relation to the sinking of the vertebral plates was observed.

Abdominal ultrasound with multifrequency convex probe was performed after denying drug and material allergies. The results confirmed a liver of normal size and echogenicity and a normal gallbladder and biliary tract. The pancreas and spleen were without alterations. Kidneys were well-located, with cortico-medullary differentiation without ectasia. The bladder was at half repletion without alterations in its wall. The following image, (Figure 3) are radiological controls.

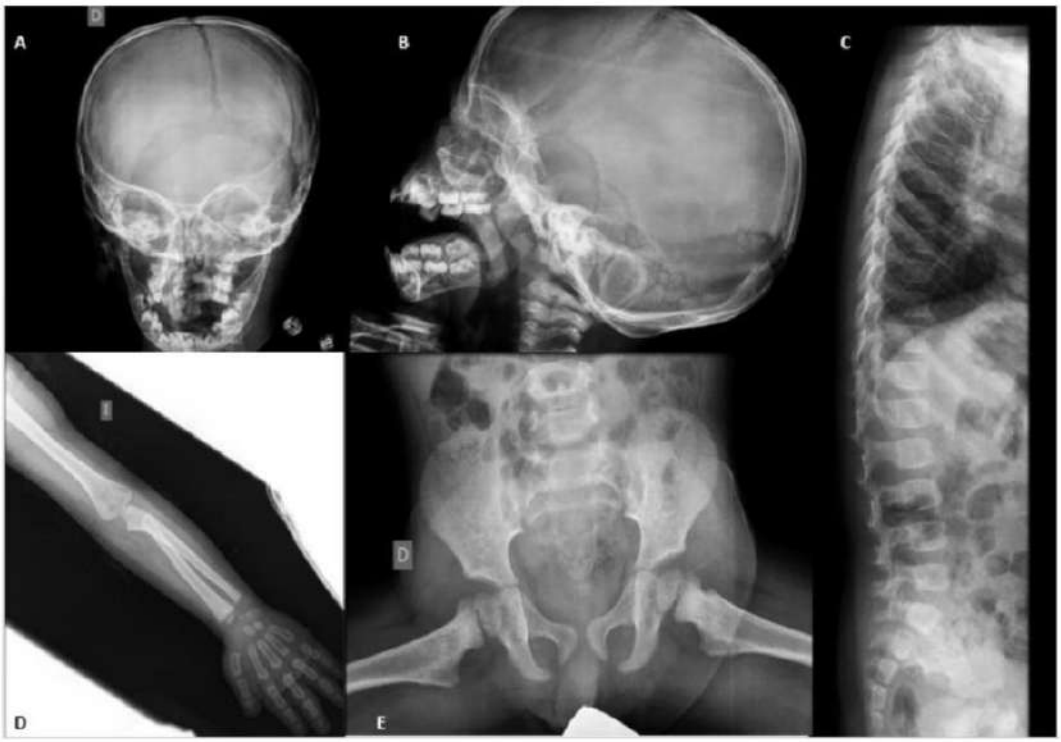

Figure 3. *Cont.*

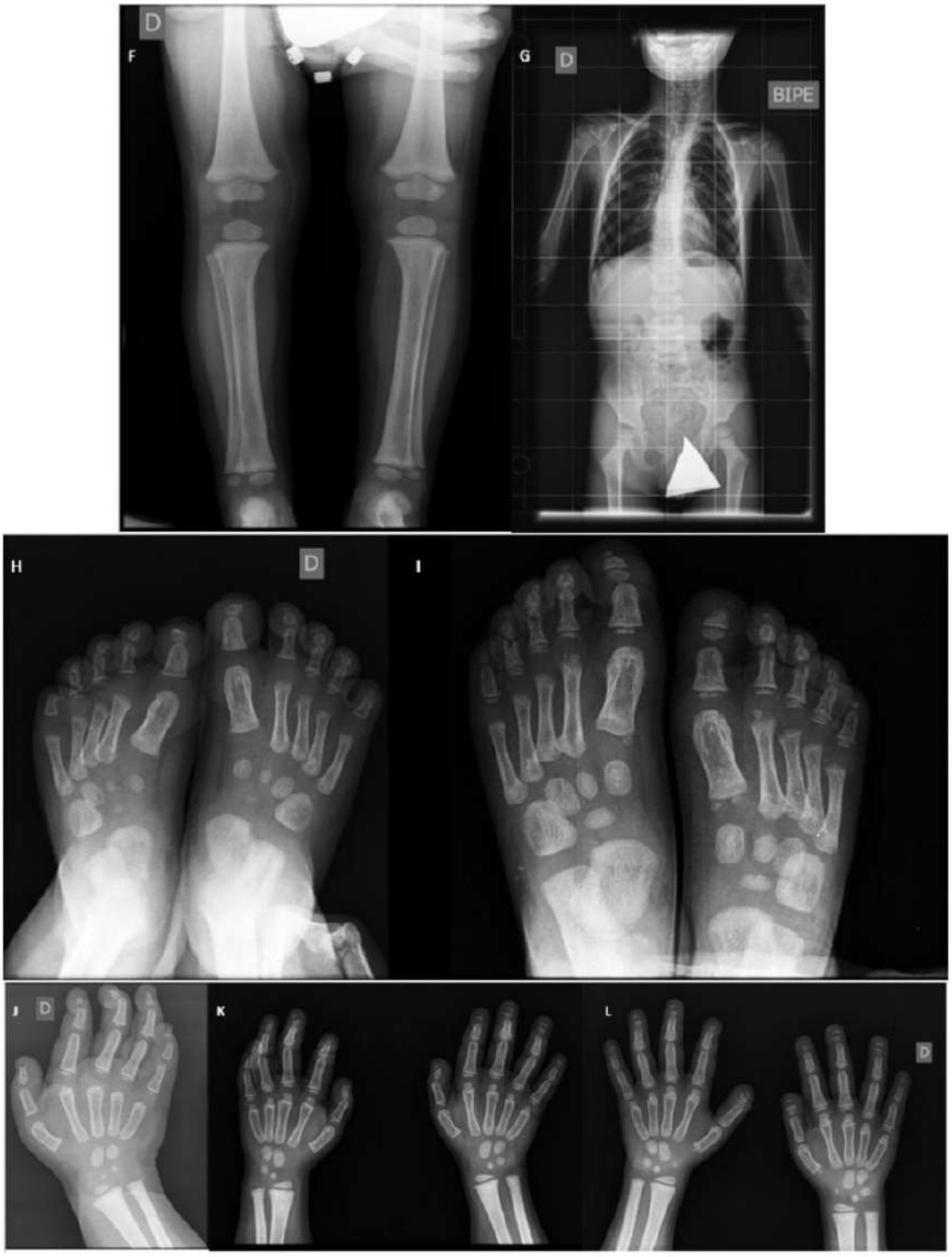

Figure 3. Radiological controls. (**A**) Skull, year 2012. (**B**) Lateral skull, year 2012. (**C**) Spinal column, year 2012. (**D**) Left arm, year 2013. (**E**) Pelvis, year 2013. (**F**) Legs, year 2014. (**G**) Standing position, year 2015. (**H**) Feet, year 2012. (I) Feet, year 2016. (**J**) Hands, year 2012. (**K**) Hands, year 2014. (**L**) Hands, year 2016.

4. Endocrine Aspects

The patient is referred to this service for growth control and osteoporosis prevention.

With regard to growth development, there is a certain delay that affects both weight and height, with most of the measurements taken being below the appropriate percentile. The following table (Table 1) shows the growth development.

Table 1. Growth development.

DATE	WEIGHT kg	SIZE cm
Newborn	4.340	54
2 years and 6 months	12	89.7
5 years	15.5	105
6 years and 8 months	18	117
10 years and 1 month	24.6	131.9
10 years and 8 months	26.4	134
11 years and 1 month	26.3	135.4

For the prevention of osteoporosis, densitometries were performed continuously in order to know the progression of osteoporosis and to administer the appropriate treatment.

With the first densitometries, no treatment was required since all the parameters were adequate. In 2016, it was decided to start treatment with bisphosphonates due to the progression of the disease. Intravenous cycles of pamidronate and vitamin D were administered orally until 2020. The results improved, and it was decided to give a rest period and re-evaluate the administration of these drugs.

5. Respiratory Features

The patient presents respiratory noises during wakefulness and more intense ones during sleep, but without presence of nocturnal apneas. Oral breathing is predominant. He sleeps in a lateral ulna position, and in early infancy in a supine position, with neck hyperextension. Striking hyporexia was detected without previous physical effort. A cutaneous and systemic anaphylactic reaction to peanut and walnut was described, as well as an allergy to the fungus *Alternaria alternate*. He has an intolerance to lentils, manifested by abdominal pain. No known drug allergies were reported. Rhinosinus infections are frequent, with abundant mucus, cough and pneumonia. Sleep oximetry was evaluated, and the results confirmed that there is no obstructive sleep apnea syndrome. In infectious processes, gastroesophageal reflux is enhanced, without morning halitosis. He tolerates exercise well.

6. Cardiological Aspects

A cardiological study was performed as a preventive measure since the description of the disease is associated with cardiac alterations. Echocardiography showed a nonhypertrophic LV (left ventricle), nondilated with normal function. There was no MR (mitral insufficiency); no gradient in LVOT (left ventricular outflow tract tachycardia); a normal RV (right ventricle); and no IT (tricuspid insufficiency). A systolic murmur was detected. The sinus rhythm's frequency is in normal ranges. The patient is normotensive.

In 2018, a jugular protrusion was observed at the jugular level that increased when coughing. A CT angiography was performed. A PDA (permanent ductus arteriosus) with a length of 12 mm was detected. The aortic end measured 3.6 × 2.7 mm; and the pulmonary end, with a filiform passage, measured 0.6 mm. The right jugular vein was dilated and tortuous. The PDA had no hemodynamic repercussions. In 2021, percutaneous closure was performed and the evolution was favorable.

7. Neurosurgery Aspects

He was referred to this service for evaluation for craniofacial malformation syndrome due to Wormian bones and Chiari propensity. After one year of age, hand deformity and delayed lambdoid closure with increased spaces in the lambdoid sutures appeared. Radiological control was performed. A metopic ridge, lower-third hypoplasia, low-set ears and fusion defects in lambdoid sutures were seen, as well as hypertrichosis in the dorsal and lumbar regions. There were no fusion defects in the posterior arches. The fingers had short and wide phalanges, which were also in the feet, and were more striking in the first finger. Craniospinal MRI and renal ultrasound were requested to evaluate associated malformations.

8. Neurology Aspects

At one and a half years of age, a study was carried out in this service, which showed an autonomous gait from 12 months of age and adequate crawling from 9 months of age. Handling was good and he used a mother–dad language. The neonatal screening was normal, with no incidences. Hearing was normal, although the test was repeated twice due to doubts. Gait was somewhat unsteady, but muscle strength and mass were normal. The myotatic reflexes had a slight increase in the reflexogenic area in the thighs. CPR (plantar cutaneous response) was observed in flexors. There were no signs of cerebellar dysfunction. There was hypotonia, probably related to mild joint hyperlaxity.

At 2 years and 11 months, the disease continued to progress normally. There was some delay in expressive language, with abundant jargon but the ability to make a sentence and good verbal comprehension. He would receive support in his school and treatment with a speech therapist. He was referred to the early care service to perform a Battelle test.

9. Early Care

A screening test, Battelle [27], was performed at 32 months. It is a tool aimed at assessing global development in several specific areas. There were no deficits in the adaptive, gross motor, fine motor and cognitive areas. He was at −1 standard deviation from the measurement in the total motor area and at −1 standard deviation from the measurement in the personal social, receptive and total areas. He was more than −2 standard deviations away from the measurement in the areas of expressive and total communication. All are shown below in Figure 4 and Table 2.

Table 2. Age equivalence by area.

	Personal-Social	Adaptive	Gross Motor	Fine Motor	Total Motor	Receptive	Expressive	Total Comunication	Cognitive	Total Score
Age equivalent in months	23	27	27	24	25	24	17	20	32	24

Currently, the evolution of language is favorable; he improves in communication and is able to make sentences. He presents some dyslalia. He has good social interaction.

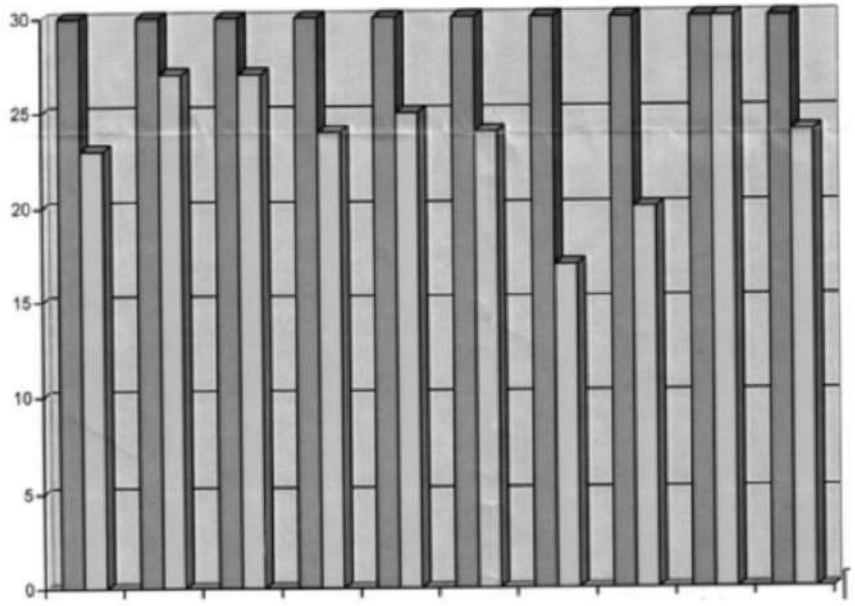

Figure 4. Battelle test graph.

10. Ophthalmological Aspects

In this service, a study is performed to identify possible pathological findings at ocular level. A fundus examination was performed, where ocular proptosis with blue and megalocorneal sclerae was confirmed. In addition, a vision control was performed, detecting 5 diopters in the left eye and 5.5 in the right eye. He needs glasses for correction.

11. Otorrine Aspects

The patient underwent a study in this service because he presented repeated upper respiratory catarrh. He was a nocturnal snorer, without apneas but with characteristic postures. An otoscopy was performed, where wax plugs were observed in both ears. In the study of the oral cavity and oropharynx, there were grade IV tonsils (narrow isthmus of the fauces). He underwent surgery on two occasions for placement of auditory drains. In the second intervention, they were left permanently. His vegetations were also operated on by this service. The auditory potentials do not show signs of hearing loss at the moment. The results are shown in Figure 5.

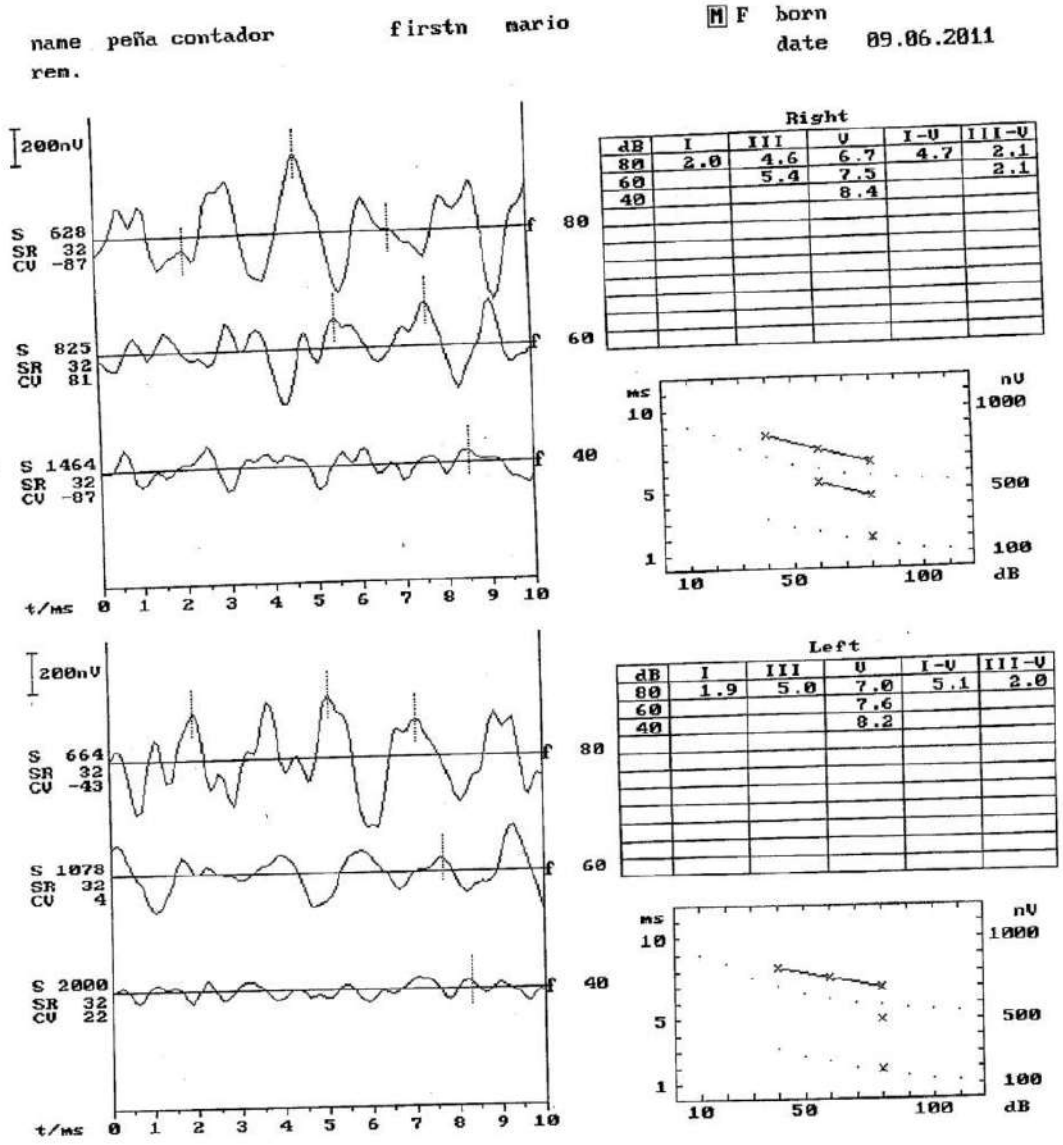

Figure 5. Auditory potentials.

12. Maxillofacial Features

The teeth began to erupt at 4 years of age, with some alteration in their alignment. The total eruption of the teeth was not complete until 7 years of age. At the age of 10, the removal of teeth was necessary to facilitate the eruption of the permanent dentition.

13. Gait Study

A gait study was performed. On visual examination, a bilateral Trendelenburg gait or "waddling gait" was observed. In addition, a significant valgus of the feet was also visually observed, which is very evident when barefoot. There is no difficulty in muscle recruitment, except when rising from the horizontal position. There, he shows difficulty in abdominal recruitment and other groups of the trunk flexion pattern, compensating in the activity with the help of the arms to perform it successfully. No sensory alterations have

been observed in fine or gross sensibility, as well as in proprioception. Reflexes are present and symmetrical, with low response. There are no dysmetria or coordination problems.

There is a very pronounced valgus in both feet, which when weight is shifted monopodally does not allow an ideal alignment, so the reaction forces of the ground allow a straightening reaction in this type of support.

In view of the above, it was decided to treat the muscular hypotonia by means of focal vibration axially on the trunk muscles, hippotherapy and work in the swimming pool.

After the focal vibration treatment, a significant improvement in gait was observed, with a gait without Trendelenburg and with a faster step cadence and longer steps, as can be seen in Video 1.

14. Psychosocial Aspects and Lifestyle

At present, the patient is perfectly adapted to his environment. He has a structured and functional family, and is integrated in the educational center. He attends the academic course corresponding to his age. He enjoys his group of friends and has developed social skills. He has correct handling and use of technology. He attends musical percussion classes at levels more advanced than his age and has a highly developed sense of rhythm and music.

15. Milestones

Table 3 shows the main milestones of the case described above.

Table 3. Main milestones in the description of the case.

Birth	2011
Diagnosis	2013
Beginning of therapy with early care	2014
Use of glasses	2014
Use of corrective insoles	2015
Initiation of bisphosphonate therapy	2016
Detection of PDA	2018
Focal vibration treatment	2021

16. Prognosis

The prognosis of patients affected by HCS will depend on the severity of the disease, clinical complications and the degenerative evolution of each patient. Generalized osteoporosis and the development of acroosteolysis will lead to fractures, difficulty in ambulation and dependence for daily living activities. The most frequent complications in this disease are basilar invagination, which will lead to neurological alterations or thoracic deformity causing ventilatory restriction.

17. Therapeutic Intervention

The therapeutic intervention in this case can be divided into several lines of action.

Regarding the pharmacological line, treatment with bisphosphonates for the improvement and prevention of osteoporosis is worth mentioning. In addition, vitamin D was administered for the same purpose. All of the underlying problems of this disease that appeared were treated with existing conventional pharmacological treatments: analgesia for pain; antibiotic therapy for infectious processes; bronchodilators for respiratory processes.

Surgical treatment in this case was performed to treat PDA, and the placement of ear drains and vegetations was identified during its clinical course.

The self-care recommendations are aimed at maintaining physical and intellectual activity as much as possible and avoiding overweight as a preventive method against the development of the disease.

A pioneering treatment for this type of patient is focal vibration (vibrotherapy). This consists of the application of a type of mechanical vibration by means of a specific vibration apparatus at a superficial level on tendons or muscles. Electronic vibrators can be used to modify different treatment parameters such as frequency, amplitude or pressure. It serves as an agent of stimulation of muscular and cutaneous mechanoreceptors within the framework of movement reprogramming. It represents an excellent passive re-education tool due to its action on the active elements of the joint [28].

In this case, the patient has limitations in certain activities such as changing and maintaining the position of the body. He is able to perform the usual daily transfers without assistance, but needs support on joining his upper limbs to sit from a supine position. In addition, he is able to move without difficulty in all types of environments, although the gait pattern is accentuated in situations of effort or uneven terrain. He has the ability to run at low speed.

As seen in Video 1, the patient's gait improves after the vibrotherapy session. As seen in the image, on the left side the patient is presented before the session and on the right side after the session.

Therefore, gait improvement is essential for this patient. Focal vibration is the treatment of choice for this purpose. It is also used in patients with muscular spasticity diagnosed with cerebral palsy.

18. Discussion

One of the main problems observed in the world of rare diseases is the delay in diagnosis [29]. This has a negative impact on the clinical approach to the disease, plunging the patient into a situation of uncertainty and chaos. On average, it can take a patient 4–5 years to obtain a diagnosis. Approximately 20% of patients take approximately 10 years to obtain a diagnosis [30]. In most cases, there is a delay in diagnosis due to the general lack of knowledge in the field of rare diseases, difficulties in accessing the necessary information and an insufficient number of professionals and specialized health centers, in addition to the low prevalence and clinical links between these pathologies.

The case described in this report does not comply with the aforementioned statistics. In this case, only 2 years were necessary to obtain a definitive diagnosis, since the phenotype and the clinical presentation were very evident.

Guidance to diagnosis is made by observation of the phenotype and clinical presentation [22]. Normally, in the process of the diagnostic phase, clinical links are found with other diseases, with which a differential diagnosis must be made [23] before starting the genetic study. This is the case of the patient described by Herrmann et al. [31], who during the diagnostic stage was suspected of pycnodysostosis [32] because of the clinical similarities that existed.

With a concise diagnostic orientation, a genetic study was performed [24]. In the case of our patient, sequencing of exon 34 of the NOTCH2 gene was performed in 2013, by means of a blood extraction. The result was a heterozygous deletion of 18 nucleotides, which justifies the diagnosis of this syndrome [6]. Unlike other mutations described in some studies [33,34], this type of mutation had not been previously described in the spectrum of Hajdu-Cheney syndrome, so there are no previously described cases that share this variant.

The pathological picture presented by the patient described in this article brings together the three essential characteristics of Hajdu-Cheney syndrome, the phenotypic variability, the degenerative character and the picture of generalized osteoporosis and acroosteolysis of the distal phalanges.

Due to the variability of NOTCH2 expression, there is a variability in the phenotypes of this type of patient that becomes evident when making comparisons with other described cases. The patients described by Swan et al. [35], Ades et al. [36] and Takatani et al. [37] stand out, where differences in physical and clinical appearance are appreciated, despite having the same diagnosis.

The degenerative character is identified in most of the cases published in the scientific literature. One of the most obvious examples is described by Harnasch H. [38]. It is true that for the observation of the degenerative character there must be a follow-up over time, an aspect that with the age of our patient is complicated to verify. In spite of the 11 years of the case presented, degenerative nuances observed at a musculoskeletal level are identified in the radiological findings in the same way that they are seen in the cases described in pediatric patients [34]. Table S1 of the Supplementary Material contains a list of the most relevant published cases of this disease diagnosed in pediatric age (less than 15 years old).

The acroosteolysis of the distal phalanges and generalized osteoporosis described are present in the majority of diagnosed cases of this syndrome, highlighting the cases of Rosenmann et al. [39], Elias et al. [40] and Bruckner et al. [41], where they justify that the most prevalent signs are acroosteolysis and generalized osteoporosis.

At the musculoskeletal level, in addition to osteoporosis and acroosteolysis, craniofacial alterations are observed, as in the cases described by Letchumanan et al. [14], Stathopoulos et al. [42] and Nunziata et al. [43]. Biconcave vertebrae are also seen in the cases described by Vissarionov et al. [44] and Chawla [45].

Deformities in hands are observed, as in the cases described by Jiménez et al. [46], Shurtleff et al. [47], Brown et al. [13] and Ventosa et al. [48] in feet, highlighting this finding in the patients of Greenberg et al. [49] and Colmenares Roldán et al. [50].

The genu recurvatum presented by the patient was previously described on different occasions by authors such as Williams [51] and Weleber et al. [52].

Kyphosis and scoliosis hinder gait, an aspect that is described in the patient of Rosenmann et al. [39], forcing our patient to use corrective insoles and vibrotherapy treatment to improve gait. Another aspect that our case also shares with the case of Rosenmann et al. [39] is the presentation of the nails in watch glass.

Growth retardation was justified in the report of Siklar et al. [16], who described the relationship between growth hormone and short stature in these patients.

Regarding the frequent rhinosinus infections presented by our patient, cough and pneumonia processes can be observed in the cases of Williams [51] and Sasaki [53].

Congenital heart disease is frequently found in the clinic of this syndrome, as in the case of Sargin et al. [18]. In one of the examinations, our patient was found to have a systolic murmur, and later, by means of an Angiotac, he was diagnosed with PDA.

The dentition abnormalities present in this case are also seen in the cases of Shaw [54] and Lee et al. [55]. Also highlighted are the studies of Bazopoulou-Kyrkanidou et al. [15] and Antoniades et al. [56] on dental alterations. Another significant work on dental restorations in patients with this syndrome was that of Vingerhoedt et al. [57].

It should be noted that aspects such as food allergies to peanuts, walnuts or lentils and the *Alternaria alternate* fungus have not been previously described in any of the cases published on this disease, in addition to the optical characteristic presented by the patient, the blue sclerae.

There is currently no curative and effective treatment for this pathology. It is true that there are studies that address this aspect, namely those by Sakka et al. [58] and Pittaway et al. [26], who worked with biosphonates, those being the treatment of choice in the case described. Specifically, the drug of choice for our patient was Pamidronate, in the same way as for the patients of Tsinopoulou et al. [59] and Al-Mayouf et al. [60].

At the surgical level, the work of Murtagh-Schaffer et al. [61] on spinal reconstructions is noteworthy, which has some relation with the signs detected in our patient at the structural level.

In this case, self-care recommendations are proposed, such as maintaining physical and intellectual activity as much as possible and avoiding overweight as a preventive method against the development of the disease.

For postural hygiene and gait improvement, our patient has been treated with vibrotherapy with very positive results. This therapy is not applied as the treatment of choice

in any of the cases described in the scientific literature. It is a possible line of future research for the development of this pathology.

The current treatment for HCS is aimed at addressing the complications and underlying problems, offering an improvement in quality of life and life expectancy [25].

This study reflects the existence of the three generalities that characterize Hajdu-Cheney syndrome. In the last 70 years, only about 100 diagnosed cases of this rare disease have been described. In view of the low prevalence of the syndrome, the description of confirmed and updated cases such as the one presented today is essential.

In particular, the contribution of this case to the scientific literature and to the development of the disease is based on the presentation of a mutation never described before. This new variant adds two previously undescribed aspects to the disease phenotype: bluish sclerae and the presence of allergies with systemic repercussions. However, it is true that with the description of only one case with these features, it is too early to speak of their inclusion in the definitive phenotype of the syndrome.

Another aspect that deserves attention is the choice of vibrotherapy as a treatment for gait reeducation in this type of patient with muscular hypotonia.

In spite of the existing advances, a complete and updated description of the phenotype of this disease, including a large sample, is still necessary.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11175205/s1. Video S1: Results after vibrotherapy session. Figure S1: Family genogram. Table S1: List of the most relevant published cases of this disease diagnosed in pediatric age (less than 15 years old). References [62–67] are cited in the supplementary materials.

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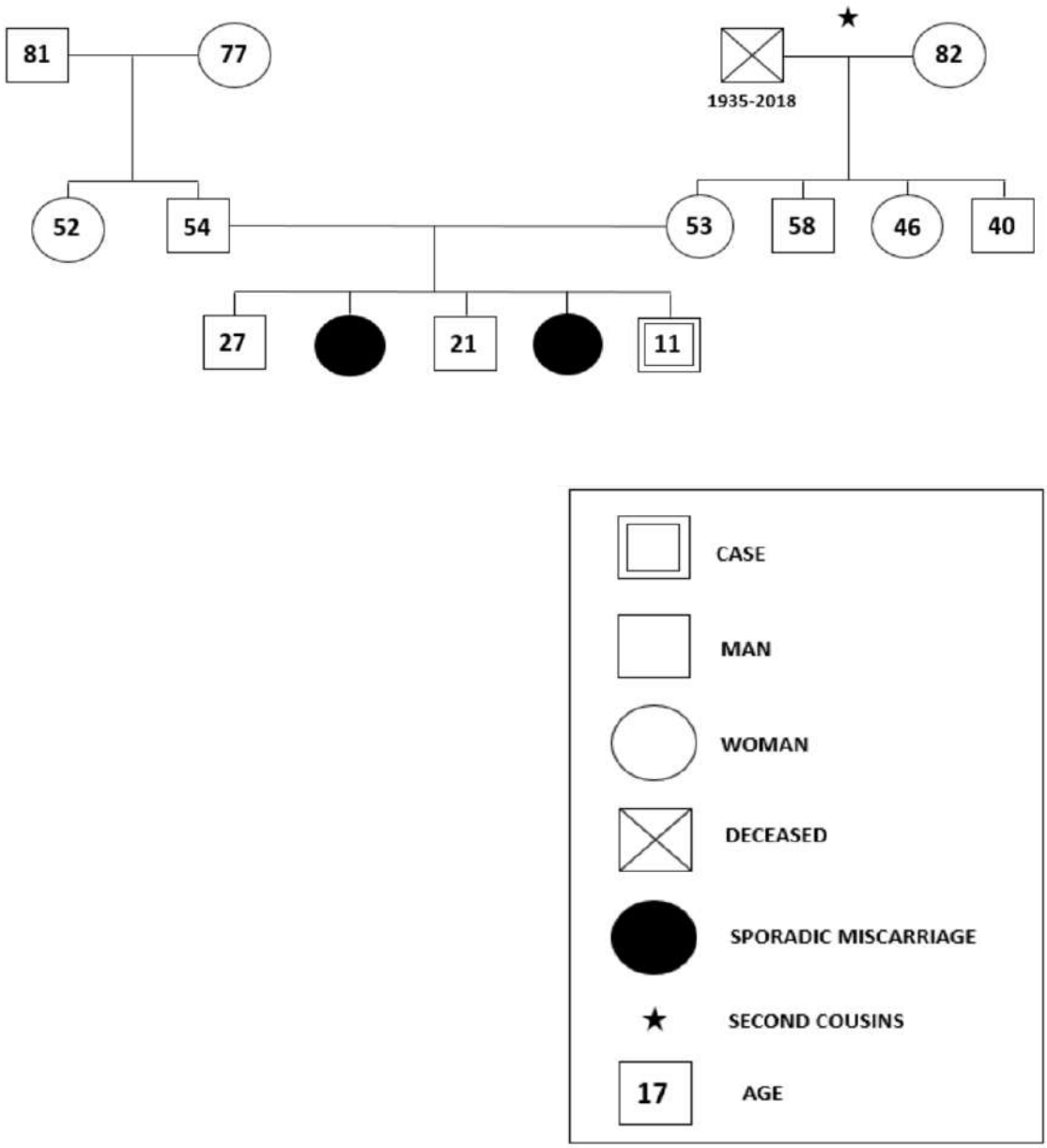
MATERIAL SUPLEMENTARIO CAPITULO IV



Genograma familiar

AUTHOR	ARTICLE	YEAR OF PUBLICATION	PATIENT NUMBER	PATIENT´S AGE	SEX	COUNTRY
Shurtleff DB et al. [1]	*Hereditary Osteolysis With Hypertension and Nephropathy.*	1964	1	4	MALE	UNITED STATES
			2	6	FEMALE	UNITED STATES
			3	8	FEMALE	UNITED STATES
Herrmann et al. [2]	*Arthro-Dento-Osteo Dysplasia (Hajdu-Cheney Syndrome)*	1973	4	10	MALE	UNITED STATES
Brown et al. [3]	*The acro-osteolysis syndrome: Morphologic and biochemical studies.*	1976	5	7	FEMALE	UNITED STATES
Weleber et al. [4]	*The Hajdu-Cheney syndrome Report of two cases and review of the literatura.*	1976	6	12	FEMALE	UNITED STATES
			7	12	FEMALE	UNITED STATES
Rosenmann et al. [5]	*Sporadic Idiopathic Acro-Osteolysis with Cranio-Skeletal Dysplasia, Polycystic Kidneys and Glomerulonephritis A case of the Hajdu-Cheney syndrome.*	1977	8	15	MALE	ISRAEL
Elias et al. [6]	*Hereditary Osteodysplasia with Acre-Osteolysis (The Hajdu-Cheney Syndrome).*	1978	9	12	MALE	UNITED STATES
Zeman et al. [7]	*Hajdu-Cheney syndrome in a 3% year old girl.*	1994	10	3.5	FEMALE	AUSTRALIA
Brennan et al. [8]	*Hajdu-Cheney Syndrome: Evolution of Phenotype and Clinical Problems.*	2001	11	5	FEMALE	UNITED STATES
			12	5	FEMALE	UNITED STATES
Antoniades et al. [9]	*Hajdu-Cheney syndrome (acro-osteolysis): A case report of dental interest.*	2003	13	9	MALE	GREECE

August et al. [10]	*Anesthesia for a child with Hajdu-Cheney syndrome.*	2009	14	8	FEMALE	UNITED STATES
Yamaguchi et al. [11]	*A case report of anesthesia for a child with Hajdu–Cheney syndrome.*	2013	15	10	FEMALE	JAPAN
Ventosa et al. [12]	*Acro-osteolysis in a 4 year-old patient: clinical features of Hajdu-Cheney syndrome.*	2013	16	4	MALE	SPAIN
Battelino et al. [13]	*End-Stage Renal Disease in an Infant With Hajdu-Cheney Syndrome.*	2016	17	8	MALE	SLOVENIA
Sakka et al. [14]	*Bone Structural Characteristics and Response to Bisphosphonate Treatment in Children With Hajdu-Cheney Syndrome.*	2017	18	15	MALE	UNITED KINGDOM
			19	6.8	MALE	UNITED KINGDOM
			20	7.8	FEMALE	UNITED KINGDOM
			21	10.8	FEMALE	UNITED KINGDOM
			22	10	MALE	UNITED KINGDOM
			23	13	FEMALE	UNITED KINGDOM
			24	15	MALE	UNITED KINGDOM
Ruo-Lan Gong et al. [15]	*A Novel Mutation of Notch homolog protein 2 gene in a Chinese Family with Hajdu-Cheney Syndrome.*	2017	25	4	MALE	CHINA
		2018	26	6	FEMALE	LONDON

Pittaway et al. [16]	*Bisphosphonate therapy for spinal osteoporosis in Hajdu-Cheney syndrome – new data and literature review.*		27	8	FEMALE	LONDON
			28	11	FEMALE	LONDON
			29	15	FEMALE	LONDON
Graversen et al. [17]	*Phenotypic presentations of Hajdu-Cheney syndrome according to age – 5 distinct clinical presentations.*	2019	30	10	FEMALE	DENMARK
Jiménez et al. [18]	*Hand Deformities in Hajdu-Cheney Syndrome: A Case Series of 3 Patients Across 3 Consecutive Generations.*	2020	31	6	MALE	SPAIN

Lista de los casos publicados más relevantes diagnosticados del Síndrome de Hajdu-Cheney en edad pediátrica. (Menos de 15 años).

CAPÍTULO V

Por último, el cuarto objetivo específico se consiguió tras realizar un plan de cuidados estándar de enfermería específico para el Síndrome de Hajdu-Cheney.

El plan de cuidados fue redactado con formato de artículo y publicado con el título:

Nursing Care Plan for Patients with Hajdu–Cheney Syndrome.

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Article

Nursing Care Plan for Patients with Hajdu–Cheney Syndrome

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Abstract: Hajdu–Cheney syndrome is a rare genetic disease. Its main features include phenotypic variability, age-dependent progression and the presence of acroosteolysis of the distal phalanges and generalized osteoporosis, which have significant disabling potential. Currently, there is no effective curative treatment, so nursing care is essential to ensure the maintenance of the quality of life of these patients. The main objective of this study was to establish a specific standardized nursing care plan using the NANDA–NIC–NOC taxonomy. The application of a care plan as such would improve the quality of life of patients affected by this rare disease, will contribute to increasing healthcare professionals' knowledge on this matter and will support future studies on this disease.

Keywords: rare disease; Hajdu–Cheney syndrome; nursing care plan; acroosteolysis; NOTCH2; clinical practice; healthcare

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1. Introduction

To date, more than 7000 rare diseases have been described around the world, yet very little scientific knowledge has been generated for only about 800 of them. Eighty percent of rare diseases have a genetic origin and have high mortality rates [1]. By definition, rare diseases have a low prevalence in the general population, and Hajdu–Cheney syndrome (HCS) specifically has very few reported cases [2]. These cases are presented in the context of limited and dispersed study samples, with variable phenotypes and clinical manifestations that have not been clearly documented and show different clinical courses [3].

Considering the clinical and scientific panorama where this disease makes its appearance, it is important to note that standardization and universalization of specific practices and diagnostic tests would simplify the workflow and significantly contribute to the advancement of research. A detailed description of cases would contribute to reducing the time to diagnosis, improve the quality of treatments and offer better overall assistance to each patient. An update of the cases already reported would be of great help to carry out a cross-sectional study from a new standpoint, offering a better, more global perspective of this disease. For this reason, a closer consideration of the phenotypic differences, the clinical presentation and courses the disease takes in each patient and the development of a specific intervention plan for HCS patients would make the management of this disease more effective and straightforward [4].

Currently, there is no effective curative treatment for this disease, so nursing care is ever more important to ensure the maintenance of the quality of life and well-being of these patients, their families, caregivers and friends.

There are no scientific publications that focus solely on nursing care and the role of nurses in the care of patients diagnosed with Hajdu–Cheney syndrome. A specific

standardized nursing care plan for this disorder will update knowledge in this field and will contribute to an improvement in quality of care by enabling better management of the disease, leading to an improvement in the quality of life of these patients and their families.

Background

Hajdu–Cheney syndrome was first described by N. Hajdu in 1948 [5], and the description was completed at a later date by D. Cheney in 1965 [6]. Since then, approximately 100 cases have been reported worldwide, which has led to the identification of the three main features that are shared by all patients: phenotypic variability [7], age-dependent progression [3] and the presence of generalized osteoporosis and acroosteolysis of the distal phalanges as well as other clinical manifestations [8].

This syndrome is classified as a rare genetic disease, with classification references ORPHA955 in the ORPHANET database [2] and #102500 in the OMIM database [9]. It mainly affects the connective tissue and belongs to the osteolysis syndromes group [10].

It is caused by a heterozygotic mutation of the gene NOTCH2 [11] located on chromosome 1p13-p11. This gene is closely linked to skeletal development [12], so alterations at this level will lead to skeletal disorders. This disease follows an autosomal-dominant inheritance pattern [13], although descriptions of cases with sporadic mutations can be found [14]. As in many other rare diseases, the prevalence of HCS is less than one in one million live births (<1/1,000,000) [2].

A definitive diagnosis is reached by genetic sequencing, although the initial diagnosis is suspected based on the observation of phenotype and radiological findings [15]. Due to the phenotypic variability, on occasion, other syndromes may have to be included in the differential diagnosis as there are certain overlapping features with diseases such as Alagille syndrome or lateral meningocele [16,17].

Considering the degenerative nature and the phenotypic variability of this disease, it is practically impossible to observe the complete and definitive phenotype of the disease in a single person. The clinical signs and symptoms appear in different bodily systems. Some of the frequently found clinical manifestations include cranial and facial alterations [5], premature denture loss [18], short stature [19], joint laxity, cervical instability [20], osteolysis of the distal phalanges and generalized osteoporosis [21]. Other clinical manifestations may include cardiovascular alterations [22], renal impairment [23], delayed motor development and hearing and sight loss [24], among others.

Some of the clinical complications that have been found in this syndrome include basilar invagination [5], hydrocephalus [25], vertebral collapse due to compression [26] and ventilatory restriction due to thoracic deformities [27].

Hajdu–Cheney syndrome is classified as a severe rare disease; however, no studies offer a global perspective of the disease regarding prognosis and quality of life of the affected patients. The severity of the disease depends on the organs and systems that are affected, the clinical complications and the degenerative progression of the disease in each patient. The generalized osteoporosis and the development of acroosteolysis are responsible for fractures, difficulties in walking and dependency for activities of daily living.

Prognosis worsens when complications such as basilar invagination exist, causing neurologic alterations or thoracic deformities that cause ventilatory restriction. Due to the low prevalence of HCS and the scarcity of qualitative information on this syndrome, it is difficult to determine the burden of disease and years of healthy life lost.

Currently, there is no definitive or effective treatment for HCS. Studies on pharmacological treatments for this disease show no clear evidence on their efficacy. Bisphosphates are the drug group of choice in certain cases [28,29], whereas surgical treatment generally aims to alleviate certain clinical findings and complications [30].

As there is no definitive treatment for this disease, management of this syndrome focuses on offering the best care available to improve the quality of life and life expectancy of these patients.

Nursing professionals are responsible for offering evidence-based quality care in order to guarantee the well-being of these patients and their families. This fact relates to the objective of this study, considering that no nursing care plans that standardize care for these patients have been developed to date. Having a plan of such characteristics would be of great help for nursing practice, for health education and for better management of this disease.

The main objective of this article is to present a standardized care plan specifically for patients diagnosed with Hajdu–Cheney syndrome that will impact the approach in management and care in this disease and, therefore, the quality of life of these patients and their families.

2. Materials and Methods

Throughout the development of this report, nursing methodology was consistently applied—in other words, a direct application of the scientific method of nursing care [31]. It is a systematic process known as the "Nursing Care Process" [32], which establishes a framework for offering rational, logical and efficient care by focusing on achieving expected outcomes by means of a series of interventions. It is an organized method that is classified as a deductive theory as of itself and is considered a quality standard in professional practice. Therefore, the nursing profession is a legitimate scientific discipline [33].

This standardized nursing care plan for Hajdu–Cheney syndrome has been developed following the guideline of the "Nursing Care Process". It aims to ensure the quality of the care and provides the basis for operational control and the means for systemizing and performing research in this field. The process outlines five phases: evaluation, diagnosis, planification, execution and assessment [31]. By applying this method, the needs of each patient will be detected, problems will be identified and solutions will be proposed by offering evidence-based nursing care. Once problems have been identified, concrete goals and outcomes should be set, alongside the proposal and planification of specific interventions to aid in reaching said goals.

It is necessary to emphasize that this report presents a standard nursing care plan for patients diagnosed with Hajdu–Cheney syndrome. Therefore, before its implementation, it is essential to adapt and personalize each of the five phases that make up the care plan for the specific patient. The development of the last two phases, execution and assessment, will depend directly on the implementation of the plan, being different for each specific patient.

2.1. Evaluation

Evaluation is the first phase of the Nursing Care Process. In this phase, the basic needs of the patient, their family and their environment are determined, information which is essential in establishing a problems diagnosis [32].

The evaluation established in this nursing care plan was developed following the system designed by Marjory Gordon [34]. It is a system the fulfills all the criteria needed to carry out an effective nursing evaluation, so it constitutes a useful evaluation tool in any nursing discipline module. It defines eleven functional patterns as established behaviors that are shared by all human beings and which contribute to their health and quality of life over time and independent of age and disorders.

In order to detect needs in this phase, a review of the literature [4] was carried out with the aim of obtaining a complete knowledge of the syndrome. In total, 115 described cases published from 1948 to 2022 were analyzed, and 12 patients with a confirmed diagnosis were contacted directly [35].

2.2. Diagnosis

During the diagnosis phase, the problems that arise from the specific needs are identified. Considering how the different functional patterns are affected and using the NANDA [36] taxonomy, a classification into real or potential problems is made, as well

as differentiating problems relating to autonomy, nursing diagnoses and collaboration issues [37].

2.3. Planification

Once the problems have been identified, a care plan is developed with the aim of providing solutions to the problems. Standard outcomes are established which will be reached by means of a series of interventions. In this case, the guidelines followed for the writing of the objectives and interventions are the NOC [38] and NIC [39] taxonomies.

In addition to the previously mentioned tools used in the development of this report, we used the NNNConsult platform [40].

The organization and sequencing of the Nursing Care Process are essential for the correct development of a nursing care plan. As we pointed out earlier, this report presents a series of indications for a standardized care plan that must be adapted and tailored to each specific case before it can be implemented.

This report was presented to and gained approval from the Research Ethics Committee of the Province of Granada (Spain) in 2 March 2021.

2.4. Execution and Assessment

Both phases of the care plan must be analyzed once it has been implemented with a specific patient.

3. Results

3.1. Evaluation

The evaluation is shown in the following table (Table 1) and was designed according to the functional patterns described by Marjory Gordon [34]. In this evaluation, a series of different patterns are presented alongside specific observations regarding the disorder in question and a list of useful nursing scales for quantifying the evaluations.

Table 1. Evaluation according to Marjory Gordon functional patterns.

Functional Patterns	Observations	Proposed Scores and Scales
Pattern 1: Health perception—health management	The context of a patient diagnosed with HCS with regards to perception and health management is abnormal. Due to the high potential of disability that accompanies this syndrome, there is a deficit in autonomy in the maintenance of healthy habits involving personal hygiene and cleaning of the home. HCS patients require the help of third parties. The scarcity of knowledge surrounding the disease, delays in diagnosis and the absence of an effective treatment negatively impact the individual's perception of health. The risk of accidents, either work- or traffic-related or at home, is patent due to difficulties in walking without assistance. Numerous hospital admissions impact the alteration of this functional pattern.	-Barber [41] (risk of dependence) -Fall risk index [42] (risk of falls) -Tinetti [43] (static balance and gait balance) -Goldberg Ghq28 [44] (general health)
Pattern 2: Nutritional—metabolic	There are problems with eating due to the premature loss of dental pieces and the presence of cavities. Another factor that complicates feeding is intestinal malrotation that may be present in some patients. In certain cases, different food allergies may appear. Short stature is another clinical manifestation of this syndrome. Evaluation of skin may be abnormal as certain patients may have plantar ulcers, and HCS patients' nails are characteristically short and bulky. A generalized hirsutism may be present.	-MUST [45] (risk of malnutrition) -Norton [46] (risk of pressure ulcers) -Braden [46] (risk of pressure ulcers)
Pattern 3: Elimination	The prevalence of constipation is high in HCS patients, often requiring the use of laxatives. The presence of small polycystic kidneys limits urinary clearance. Urinary tract infections are frequent. The use of absorbent pads or diapers is common considering limited mobility issues.	-Bristol scale [47] (consistency of stools) -Bonney test [48] (urinary incontinence)
Pattern 4: Activity—exercise	Generalized osteoporosis and skeletal malformations limit mobility. Thoracic deformities impede normal ventilation. Excessive weakness. Fatigue with minimal efforts. Dependency for activities of daily living. In some cases, there are congenital heart defects and septal defects. Recurrent respiratory infections. High risk of falls due to instability when standing.	-Barthel [49] (functional assessment) -Katz [50] (autonomy for activities of daily living) -Karnofski [51] (quality of life) -Pain Visual Analog Scale (VAS) [52] (pain intensity)

Table 1. *Cont.*

Functional Patterns	Observations	Proposed Scores and Scales
Pattern 5: Sleep—rest	Chronic pain is present in all patients diagnosed with HCS, which affects falling asleep if uncontrolled. Anxiety and depression are common psychological disorders in HCS patients. The use of sleeping pills is frequent to aid falling asleep and sleep maintenance.	-Oviedo [53] (level of sleep satisfaction)
Pattern 6: Cognitive—perceptual	Delay in speech and language acquisition. Perceptive alterations such as hypoacusis and progressive vision loss. Acute pain and chronic invalidating pain. Depression.	-Pfeiffer [54] (cognitive decline) -Glasgow [55] (level of consciousness)
Pattern 7: Self-perception—self-concept	Deep voice. Limited physical abilities. Altered postural and mobility patterns.	-Gardner [56] (body image)
Pattern 8: Role—relationships	Family relationships are affected by dependency. The adaption to different scenarios may cause social rejection.	-Duke-Unc [57] (perceived social support) -Zarit [58] (carer burnout)
Pattern 9: Sexuality and reproductive	In certain cases, issues may arise during women's reproductive stage.	-
Pattern 10: Coping—stress tolerance	Stress is present in the majority of these patients due to uncertainties about the future and the numerous hospital admissions.	-Perceived stress scale [59] (stress levels)
Pattern 11: Values—beliefs	There are concerns regarding the meaning of life, death, pain and illness.	-

3.2. Nursing Care Plan

We now present the standardized specific nursing care plan for Hajdu–Cheney syndrome. Three types of problems are distinguished: autonomy problems, collaboration problems and nursing problems, reported according to the NANDA taxonomy, also known as a nursing diagnosis. Additionally, we refer to real or potential issues in each segment [37].

3.2.1. Nursing Diagnosis

The problems that are detected which are a concern for nurses are commonly referred to as a nursing diagnosis [31]. In Appendix A, we present the nursing diagnosis along with the expected outcomes (NOC) [38] after the implementation of specific interventions (NIC) [39] by means of different activities. Additionally, the diagnoses are organized according to the functional patterns used for the nursing evaluation. The distinction between real problems and potential problems is implicit in the table in the appendix.

As can be seen in Appendix A, most of the problems detected in this section are related to impaired mobility and the high disabling potential of the syndrome, which has a negative impact on other aspects. Pain is another important factor to highlight as it directly influences the development of daily routine. Furthermore, one of the main complications of this syndrome is problems related to breathing, caused by chest deformity. It is also worth mentioning the fear and anxiety in a situation of uncertainty about the health situation in the future.

3.2.2. Autonomy Problems

Autonomy problems are problems in which the independence of the patient is compromised [33]. These issues reveal a total or partial deficit in the physical or psychological ability of the patient to carry out the required actions to satisfy their needs. These problems may be temporary or permanent, but they are always classified as real. In Appendix B, we present the autonomy problems related to the interventions and nursing-specific activities following the NIC taxonomy [39].

As can be seen in Appendix B, the high disabling potential and degenerative nature of this pathology have a negative impact on the autonomy of these patients. Autonomy can compromise aspects such as feeding, elimination, mobilization and personal hygiene, among others.

3.2.3. Collaboration Problems

Collaboration problems are health problems in which the patient needs nurses to carry out specific control- or treatment-related activities that were prescribed by another healthcare provider [31]. This type of issue can be classified as real or potential. In Appendix C, we present specific collaboration issues that arise in this syndrome related to the interventions and nursing-specific activities following the NOC taxonomy [39].

Appendix C confirms that a multidisciplinary perspective is necessary to care for this type of patient. The relationships between nursing and other health fields such as medicine, psychology, physiotherapy and podiatry are evident in this section. All of them are essential for the care of patients diagnosed with this syndrome.

4. Discussion

It is of utmost importance to understand the scenario in which this disease develops so as to fully comprehend the analysis of this report from the correct perspective.

Although advances in the search for treatments, both pharmacological [28,29,60] and surgical [20,30], have been remarkable in recent years, there is still no effective curative treatment for this syndrome to date, thus highlighting the need for this report.

It is worth noting that what we present is a standardized nursing care plan, so before implementation, it must be personalized to adapt it to the specific needs of each patient and altered, if necessary, after each intervention.

The main features of this syndrome stand out after the initial evaluation. The degenerative and invalidating nature of the disease, as described by Jirecjová et al. [61] and Brennan et al. [3] in their publications, highly impacts patients' autonomy and increases their levels of dependence. The generalized osteoporosis and osteolysis of the distal phalanges, reported by numerous experts on the matter such as Brown et al. [8] and Rosenmann et al. [21], noticeably limit mobility and reduce the possibilities of walking without assistance. The general uncertainty and scarcity of knowledge that come with any rare disease generate a state of anxiety and stress that affects mental health [62].

The perception and management of health in these patients is closely related to their level of autonomy. The invalidating nature of the disorder, previously described by Descartes et al. [14] in their studies, is the reason behind the fact that most patients require assistance for everyday life activities. It is of utmost importance to highlight the role of carers and their relationship with the patient and their families and note that it is a responsibility of nursing to also care for carers. Respiratory infections, such as those presented in the cases reported by Williams et al. [63] and Sasaki et al. [64], as well as urinary tract infections, such as those described in the case report by Currarino et al. [23], are common complications, so patients and their families must be instructed on how to prevent and manage them. Mobility issues are closely linked to risk of falls, so it is important to implement exercises that work on balance, gait control and the use of walking assistance devices or mobility aids. These issues have been broadly discussed in several articles, including one by Colmenares et al. [65]. In patients who have very limited mobility and who spend long hours in bed, there is a high probability that pressure ulcers will develop if no measures are taken to prevent them. Education on pressure ulcer prevention is key, including frequent control of high-pressure areas, postural changes and the use of anti-bedsore air mattresses.

The premature loss of teeth, described in publications by Lee et al. [66] and Shaw et al. [18], as well as possible intestinal malrotation, as Hajdu [5] reported in his first description of the syndrome, are problems that generate nutritional issues and complicate management. In these cases, malnutrition must be sought and ruled out. Nursing care practices must include detection of the risk of malnutrition and education regarding healthy eating habits and oral care and hygiene. These points are discussed in depth by Vigerhoedt et al. in their study [67].

With regards to elimination, constipation is one of the most frequent symptoms in patients with HCS. Encouraging physical activity and implementing a healthy balanced

diet are key aspects in constipation prevention. In more severe cases, the use of laxatives or other drugs that increase intestinal motility may be required, as is reported in some of the cases described in the literature [35].

There is a group of patients who present with a clinical combination that is characteristic of this syndrome: polycystic kidneys and serpentine fibula. In these patients, due to the multiple cysts in their kidneys, alterations in urinary elimination may appear. Fryns et al. [68] and Ramos et al. [69] made interesting contributions on this matter.

Some of the main problems of this disease are the generalized osteoporosis and the osteolysis of the distal phalanges that develop and worsen over time [8]. Alterations in bone structures have an effect on mobility at all levels, contributing to the loss of autonomy and increasing the risk of injuries and falls, as reported by Greenberg et al. [70]. Thoracic bone deformities may limit the ventilation of basal sectors and increase the risk of infections. Extreme fatigue with minimum efforts, tiredness and strength loss also translate into limited periods of time dedicated to physical exercise.

The sleep pattern in these patients is also often affected, and many require the administration of medication to aid in falling asleep [35].

Pain management is another main issue that must be tackled by nurses treating this disorder. This issue is highlighted by Brown et al. [8] and Harnasch [71]. The identification and measurement of pain are essential for adequate pain management. Postural changes and the use of painkillers are effective tools in these situations.

The emotional state of a patient diagnosed with HCS is often related to their disease process. Anxiety and stress arise from uncertainty and fear of the future [62]. Creating safe spaces where the patients and their families can talk and share their thoughts and feelings is useful in disorders such as this. Emotional support is very important for these patients. The stress caused by the disease burden must be treated, including specific care regimes that favor family communication and facing of reality.

Social relationships often suffer due to communication issues. Improving speech clarity and hearing loss are nursing care issues that must be taken into account. Herrman et al. [24] described a case with hearing difficulties that highlights the importance of this kind of care.

Sexuality need not be affected in these cases; however, it is important to identify possible risks in the reproductive function of women affected by HCS, especially if complications have already been diagnosed, as in the case of the patient reported by Nozaki et al. [72].

Aspects relating to values and beliefs are very personal matters and difficult to consider in a standardized way.

It is worth noting once again that the nursing care plan we have proposed constitutes a standardized nursing care plan for this syndrome which must be personalized and adapted to each patient, their family and their environment before implementing it in clinical practice.

The scarcity of scientific publications and knowledge on this syndrome as well as its low prevalence are the main limitations found during the development of this study.

5. Conclusions

Prior to this study, the nursing care and management of this syndrome was lacking specific indications for the care of HCS patients, their families and their environment. The implementation of this nursing care plan would imply an advancement in the knowledge of this syndrome and an improvement in the well-being of patients. The universalization and standardization of nursing care for Hajdu–Cheney syndrome will serve as a firm basis of knowledge on which to build future lines of research on this matter.

6. Limitations

The limitations of this study are related to the low prevalence of the disease and, consequently, to the difficulty in finding a large population sample.

Occasionally, due to the specificity of the syndrome, complications arose regarding the use of the NANDA–NOC–NIC taxonomy. Another limitation encountered in conducting this study is the scarcity of scientific publications on the subject.

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Appendix A Nursing Diagnosis

Pattern 1: Perception—Health Management			
NANDA	**NOC**	**NIC**	**ACTIVITIES**
[00004] Risk of infection	[0703] Severity of infection [1902] Risk Control	[6540] Infection Control	-Teach caregivers proper handwashing -Instruct the patient on the correct hand washing techniques. -Administer antibiotic treatment when appropriate. -Teach the patient and family to avoid infections.
[00035] Risk of injury	[1912] Falls [1910] Safe Home Environment [0200] Ambulate [1828] Knowledge: Fall Prevention [1926] Safe Wandering [0202] Balance [0208] Mobility [0212] Coordinated Movement	[6490] Fall Prevention [3520] Care of pressure ulcers	-Identify cognitive or physical deficits of the patient that may increase the possibility of falls in a given environment. -Control gait, balance and fatigue when walking. -Teach the patient how to fall to minimize the risk of injury -Use an established risk assessment tool to assess the individual's risk factors (Braden scale). -Closely monitor any reddened area. -Apply protective barriers, such as absorbent creams or compresses, to remove excess moisture, as appropriate. -Inspect the skin of bony prominences and other pressure points when changing position at least once a day. -Apply protectors for the elbows and heels, as appropriate. -Teach family members/caregiver to watch for signs of skin breaks, as appropriate.

[00036] Choking Hazard	[0403] Respiratory Status: Ventilation	[3140] Airway management [3350] Respiratory Monitoring	-Position the patient to maximize ventilation potential. -Perform chest physiotherapy, if indicated. -Remove secretions by encouraging coughing or by suction. -Teach the patient to use the prescribed inhalers, if applicable. Use fun techniques to stimulate deep breathing in children (make soap bubbles; blow a whistle, harmonica, balloons; have a contest blowing ping-pong balls, feathers, etc.). -Monitor respiratory status and oxygenation, as appropriate. -Monitor the frequency, rhythm, depth and effort of the breaths. -Evaluate chest movement, observing symmetry, use of accessory muscles and intercostal and supraclavicular muscle retractions. -Watch for noisy breathing, such as stridor or snoring
Pattern 2: Nutritional—Metabolic			
NANDA	**NOC**	**NIC**	**ACTIVITIES**
[00002] Nutritional imbalance: lower than body needs	[1100] Oral Health [0303] Self-care: eating	[1100] Nutrition Management	-Determine the nutritional status of the patient and their ability to meet nutritional needs. -Identify the patient's food allergies or intolerances. -Instruct the patient on nutritional needs (i.e., discuss dietary guidelines and food pyramids).
[00046] Impaired skin integrity	[1101] Tissue Integrity: Skin and Mucous Membranes	[3520] Care of pressure ulcers [3590] Skin Watch [840] Position Change [1660] Foot care [940] Traction/Immobilization Care	-Use an established risk assessment tool to assess the individual's risk factors (Braden scale). -Closely monitor any reddened area. -Apply protective barriers, such as absorbent creams or compresses, to remove excess moisture, as appropriate. -Place on a suitable therapeutic mattress/bed. -Place in the specified therapeutic position. -Instruct the patient/family on the importance of foot care. -Cut toenails of normal thickness when they are soft, with a nail clipper and using the curve of the finger as a guide. -Refer to the podiatrist to cut thick nails, as appropriate.
[00047] Risk of deterioration of skin integrity	[1902] Risk Control	[3540] Prevention of pressure ulcers [3590] Skin Watch	-Use an established risk assessment tool to assess the individual's risk factors (Braden scale). -Closely monitor any reddened areas.
[00048] Deterioration of the dentition	[1100] Oral Health [0308] Self-care: oral hygiene	[1710] Maintenance of oral health [1730] Restoration of oral health [5510] Health education	-Establish an oral care routine. -Identify the risk of developing stomatitis secondary to drug therapy. -Teach the person to brush their teeth, gums and tongue.
[00197] Risk of dysfunctional gastrointestinal motility	[0501] Intestinal elimination [1902] Risk Control	[200] Promotion of exercise [6650] Surveillance	-Determine the individual's motivation to start/continue with the exercise program. -Explore obstacles to exercise. -Help the individual to establish the short and long term goals of the exercise program. -Monitor the individual's response to the exercise program.

[00315] Delayed infant motor development	[0208] Mobility [1308] Adaptation to physical disability	[6490] Fall Prevention [6650] Surveillance [200] Promotion of exercise	-Identify cognitive or physical deficits of the patient that may increase the possibility of falls in a given environment. -Control gait, balance and fatigue when walking. -Monitor the individual's response to the exercise program. -Determine the individual's motivation to start/continue with the exercise program.
Pattern 3: Elimination			
NANDA	**NOC**	**NIC**	**ACTIVITIES**
[00011] Constipation	[0501] Intestinal elimination [2102] Pain Level [1621] Adherence behavior: healthy diet [0208] Mobility	[450] Management of constipation/faecal impaction [466] Enema Administration [200] Promotion of exercise	-Monitor the appearance of signs and symptoms of constipation. -Identify the factors (medications, bed rest and diet) that can cause or contribute to constipation. Administer enema or irrigation, when appropriate. -Determine the individual's motivation to start/continue with the exercise program.
[00016] Impaired urinary elimination	[0503] Urinary elimination [1608] Symptom Control	[590] Management of urinary elimination [6540] Infection Control	-Observe for signs and symptoms of urinary retention. -Identify the factors that contribute to episodes of incontinence. -Explain to the patient the signs and symptoms of urinary tract infection. -Teach caregivers proper handwashing -Instruct the patient on the correct hand washing techniques. -Administer antibiotic treatment when appropriate. -Teach the patient and family to avoid infections.
Pattern 4: Activity—Exercise			
NANDA	**NOC**	**NIC**	**ACTIVITIES**
[00032] Ineffective breathing pattern	[0403] Respiratory Status: Ventilation	[3140] Airway management [3350] Respiratory Monitoring [3320] Oxygen therapy	-Position the patient to maximize ventilation potential. -Perform chest physiotherapy, if indicated. -Remove secretions by encouraging coughing or by suction. -Teach the patient to use the prescribed inhalers, if applicable. Use fun techniques to stimulate deep breathing in children (make soap bubbles; blow a whistle, harmonica, balloons; have a contest blowing ping-pong balls, feathers, etc.). -Monitor respiratory status and oxygenation, as appropriate. -Monitor the frequency, rhythm, depth and effort of the breaths. -Evaluate chest movement, observing symmetry, use of accessory muscles and intercostal and supraclavicular muscle retractions. -Observe if noisy breathing occurs, such as stridor or snoring. -Administer supplemental oxygen as ordered. -Monitor the flow of liters of oxygen.
[00033] Impaired spontaneous ventilation	[0403] Respiratory Status: Ventilation	[3390] Ventilation Aid [3350] Respiratory Monitoring [6650] Surveillance	-Monitor respiratory status and oxygenation, as appropriate. -Administer supplemental oxygen as ordered.

[00085] Impairment of physical mobility	[0200] Ambulate [0201] Ambular: wheelchair [0208] Mobility [1308] Adaptation to physical disability [0202] Balance [0206] Joint movement [0210] Perform Transfer [3110] Self-monitoring: osteoporosis [2102] Pain Level	[221] Exercise therapy: ambulation [1805] Help with self-care: aivd [1806] Help with self-care: transfer [200] Promotion of exercise [222] Exercise Therapy: Balance [6490] Fall Prevention	-Teach the patient to get into the correct position during the transfer process. -Assist the patient with the initial ambulation, if necessary. -Instruct the patient/caregiver about safe transfer and ambulation techniques. -Observe the patient's need for adapted devices for personal hygiene, dressing, personal grooming, grooming and eating. -Help the patient to accept dependency needs. -Control gait, balance and fatigue when walking.
[00093] Fatigue	[0003] Rest [1209] Motivation [0005] Activity Tolerance [2004] Physical Form	[200] Promotion of exercise [221] Exercise therapy: ambulation [226] Exercise Therapy: Muscle Control [222] Exercise Therapy: Balance [224] Exercise Therapy: Joint Mobility [6040] Relaxation therapy	-Assist the patient with the initial ambulation, if necessary. -Instruct the patient/caregiver about safe transfer and ambulation techniques. -Control gait, balance and fatigue when walking. -Determine the limitations of joint movement and its effect on function. -Protect the patient from trauma during exercise. -Create a quiet environment, without interruptions, with soft lights and a comfortable temperature, when possible.
[00102] Food self-care deficit	[0303] Self-care: eating [1308] Adaptation to physical disability	[1803] Help with self-care: feeding [1100] Nutrition Management	-Provide social interaction, as appropriate. -Provide devices adapted to facilitate self-feeding (long handles, handles with a large circumference, or small straps on utensils), if necessary. -Place the patient in a comfortable position. -Instruct the patient on nutritional needs (i.e., discuss dietary guidelines and food pyramids).
[00108] Self-care deficit in the bathroom	[0301] Self-care: bath [0305] Self-care: hygiene [0208] Mobility [1308] Adaptation to physical disability	[1801] Help with self-care: bathing/hygiene	-Provide a therapeutic environment that guarantees a warm, relaxing, private and personalized experience. -Facilitate the maintenance of the patient's routines at bedtime, signs of sleep onset and familiar objects (for children their favorite blanket or toy, rocking, pacifier or story; for adults read a book or have a pillow from home), as appropriate.
[00109] Self-care deficit in clothing	[0302] Self-care: dressing	[1630] Dress [1802] Help with self-care: dressing/grooming	-Be available to help with dressing, if needed. -Make it easier for the patient to comb their hair, if that is the case. -Encourage the patient to shave himself, as appropriate. -Maintain privacy when the patient is dressed.
[00110] Self-care deficit in the use of the toilet	[0310] Self-care: toilet use [0202] Balance [0208] Mobility	[1804] Help with self-care: urination/defecation [5606] Teaching: individual [1800] Help with self-care	-Provide privacy during elimination. -Facilitate hygiene after urinating / defecating after finishing elimination. -Provide assistive devices (external catheter or urinal), as appropriate.
[00238] Impaired standing	[0202] Balance [0212] Coordinated Movement [0211] Skeletal function [2102] Pain Level	[5612] Teaching: prescribed exercise [140] Encouraging Body Mechanics [226] Exercise Therapy: Muscle Control [222] Exercise Therapy: Balance [224] Exercise Therapy: Joint Mobility [1806] Help with self-care: transfer	-Assist the patient with the initial ambulation, if necessary. -Instruct the patient/caregiver about safe transfer and ambulation techniques. -Control gait, balance and fatigue when walking. -Determine the limitations of joint movement and its effect on function. -Protect the patient from trauma during exercise.

[00303] Risk of adult falls	[1902] Risk Control [1912] Falls [1910] Safe Home Environment	[6490] Fall Prevention	-Identify cognitive or physical deficits of the patient that may increase the possibility of falls in a given environment. -Control gait, balance and fatigue when walking.
[00306] Risk of child falls	[1902] Risk Control [1912] Falls [1910] Safe Home Environment	[6490] Fall Prevention	-Identify cognitive or physical deficits of the patient that may increase the possibility of falls in a given environment. -Control gait, balance and fatigue when walking.
Pattern 5: Sleep—Rest			
NANDA	**NOC**	**NIC**	**ACTIVITIES**
[00095] Insomnia	[2002] Personal Wellness [2000] Quality of life	[5330] Mood Control [1850] Improve sleep [2300] Medication Administration	-Assess mood (signs, symptoms, personal history) initially and regularly as treatment progresses. -Determine the patient's sleep/wake pattern. -Include the patient's regular sleep/wake cycle in care planning. -Explain the importance of adequate sleep during pregnancy, illness, situations of psychosocial stress, etc. -Follow the five rules of proper medication administration.
[00198] Sleep pattern disorder	[0004] Dream	[1850] Improve sleep	-Determine the patient's sleep/wake pattern. -Include the patient's regular sleep/wake cycle in care planning.
Pattern 6: Cognitive—Perceptual			
NANDA	**NOC**	**NIC**	**ACTIVITIES**
[00126] Poor knowledge	[0907] Preparation of information	[5510] Health education	-Determine the personal context and sociocultural history of personal, family or community health behavior. -Determine the current health knowledge and lifestyle behaviors of the individuals, family or target group. -Help individuals, families and communities to clarify health beliefs and values.
[00132] Acute pain	[1605] Pain control [2102] Pain Level	[2210] Administration of analgesics [5820] Decreased anxiety [840] Position Change	-Check the medical orders regarding the medication, dose and frequency of the prescribed analgesic. -Check the patient's previous response to analgesics (e.g., whether the non-opioid medication is as effective as the opiate). -Check previous doses and routes of administration of analgesics to avoid undertreatment or overtreatment. -Listen carefully. -Reinforce the behavior, as appropriate. -Create an environment that facilitates trust. -Place in the specified therapeutic position.
[00133] Chronic pain	[1605] Pain control [2102] Pain Level	[2210] Administration of analgesics [5820] Decreased anxiety [840] Position Change	-Check the medical orders regarding the medication, dose and frequency of the prescribed analgesic. -Check the patient's previous response to analgesics (e.g., whether the non-opioid medication is as effective as the opiate). -Check previous doses and routes of administration of analgesics to avoid undertreatment or overtreatment. -Listen carefully. -Reinforce the behavior, as appropriate. -Create an environment that facilitates trust. -Place in the specified therapeutic position

[00214] Discomfort	[2008] State of Comfort	[6482] Environment Management: Comfort [5880] Relaxation Technique	-Determine patient and family goals for environmental manipulation and optimal comfort. -Prepare the transition of the patient and family by giving them a warm welcome to the new environment. -Create a quiet environment, without interruptions, with soft lights and a comfortable temperature, when possible.
Pattern 7: Self-perception—Self -concept			
NANDA	**NOC**	**NIC**	**ACTIVITIES**
[00124] Hopelessness	[1300] Acceptance: Health Status [1206] Desire to live [1204] Emotional Balance [1209] Motivation	[5330] Mood Control [5270] Emotional support [5230] Improve coping	-Assess mood (signs, symptoms, personal history) initially and regularly as treatment progresses. -Comment the emotional experience with the patient. -Explore with the patient what has triggered the emotions. -Make empathic or supportive affirmations. -Help the patient to solve problems constructively. -Assess the patient's understanding of the disease process.
[00125] Impotence	[1702] Health beliefs: perception of control [1308] Adaptation to physical disability [1614] Personal autonomy	[5395] Improved self-confidence [5270] Emotional support	-Comment the emotional experience with the patient. -Explore with the patient what has triggered the emotions. -Make empathic or supportive affirmations. -Provide information about the desired behavior. -Help the individual commit to a plan of action to change behavior.
[00146] Anxiety	[1211] Anxiety Level [1402] Self-control of anxiety [0905] Concentration	[5820] Decreased anxiety [5230] Improve coping [6040] Relaxation therapy	-Listen carefully. -Reinforce the behavior, as appropriate. -Create an environment that facilitates trust. -Encourage the manifestation of feelings, perceptions and fears. -Identify changes in the level of anxiety. -Establish recreational activities aimed at reducing tensions. -Help the patient to identify situations that precipitate anxiety.
[00148] Fear	[1404] Fear Self Control [1210] Fear Level	[5820] Decreased anxiety [5230] Improve coping [5270] Emotional support	-Listen carefully. -Reinforce the behavior, as appropriate. -Create an environment that facilitates trust. -Encourage the manifestation of feelings, perceptions and fears.
[00153] Risk of situational low self-esteem	[1205] Self-esteem [1215] Self-awareness [1300] Acceptance: Health Status [1308] Adaptation to physical disability [1302] Coping with problems [1614] Personal autonomy	[5400] Enhancement of self-esteem [5270] Emotional support [6400] Support in protection against abuse [5240] Advice	-Determine the patient's confidence in their own criteria. -Encourage the patient to identify their strengths. Help the patient find self- acceptance. -Determine if the child/dependent adult is viewed differently by an adult based on sex, appearance, or behavior. -Identify crisis situations that may trigger abuse, such as poverty, unemployment, divorce or death of a loved one.

Pattern 8: Role—Relationships			
NANDA	NOC	NIC	ACTIVITIES
[00051] Impaired verbal communication	[0902] Communication [0907] Preparation of information	[4920] Listen Active [4974] Improve communication: hearing impairment [4976] Improve communication: speech deficit	-Show interest in the patient. -Ask questions or statements that encourage expressing thoughts, feelings and concerns. -Carry out or organize routine hearing evaluations and screenings. -Monitor the speed, pressure, rhythm, amount, volume and diction of speech. -Monitor the cognitive, anatomical, and physiological processes associated with speech capabilities (e.g., memory, hearing, and language). -Instruct the patient or family about the cognitive, anatomical and physiological processes involved in speech abilities.
[00062] Risk of caregiver role fatigue	[2205] Primary Caregiver Performance: Direct Care [2206] Primary caregiver performance: indirect care	[7040] Primary Caregiver Support	-Determine the level of knowledge of the caregiver. -Determine the caregiver's acceptance of their role. -Encourage the caregiver to participate in support groups. -Teach the caregiver health care maintenance strategies to promote their own physical and mental health.
Pattern 9: Sexuality and Reproduction			
NANDA	NOC	NIC	ACTIVITIES
[00227] Risk of ineffective maternity process	[1908] Risk Detection [2013] Balance in lifestyle	[5440] Increase Support Systems	
Pattern 10: Adaptation—Stress Tolerance			
NANDA	NOC	NIC	ACTIVITIES
[00177] Overload stress	[1212] Stress Level [1308] Adaptation to physical disability	[8340] Foster resilience [5230] Improve coping [5270] Emotional support	-Promote family support. -Facilitate family communication. -Help the patient develop an objective assessment of the event. -Make empathic or supportive affirmations. -Hug or touch the patient to provide support.
Pattern 11: Values—Beliefs			
NANDA	NOC	NIC	ACTIVITIES
[00066] Spiritual suffering	[1300] Acceptance: Health Status [1302] Coping with problems [1215] Self-awareness	[5426] Facilitate spiritual growth [5270] Emotional support [5250] Support in decision making [5240] Advice	-Show assistance and comfort by spending time with the patient, with the patient's family and with those close to them. -Encourage conversation that helps the patient organize spiritual interests. -Model healthy relationship and reasoning skills. -Make empathic or supportive affirmations. -Hug or touch the patient to provide support.

Appendix B Autonomy Problems

Problems of Autonomy		
NEED	NIC	ACTIVITIES
Feeding	[1803] Help with self-care: feeding	-Control the patient's ability to swallow. -Create a pleasant environment during mealtime (place bedpans, urinals and vacuum equipment out of sight). -Ensure the proper position of the patient to facilitate chewing and swallowing. Provide physical help, if needed. -Provide devices adapted to facilitate self-feeding (long handles, handles with a large circumference, or small straps on utensils), if necessary.

Problems of Autonomy		
NEED	**NIC**	**ACTIVITIES**
Elimination	[1804] Help with self-care: urination/defecation	-Assist the patient on the toilet/portable toilet/fracture wedge/urinal at specified intervals. -Provide privacy during elimination. -Provide assistive devices (external catheter or urinal), as appropriate.
Mobilization	[1806] Help with self-care: transfer	-Determine the patient's current ability to transfer independently (e.g., level of mobility, movement limitations, endurance, ability to stand and bear weight, medical or orthopedic instability, level of consciousness, ability to cooperate, ability to understand instructions). -Teach the patient all the appropriate techniques in order to achieve the maximum level of independence. -Teach the individual the techniques of transferring from one area to another (e.g., from bed to chair, from wheelchair to vehicle). -Teach individual the use of ambulatory aids (e.g., crutches, wheelchair, walkers, trapeze bar, cane).
Dress and Personal Grooming	[1802] Help with self-care: dressing/grooming	-Maintain privacy when the patient is dressed. -Be available to help with dressing, if needed. -Reinforce efforts to dress alone.
Maintenance of Body Temperature	[3900] Temperature regulation.	-Observe the color and temperature of the skin. -Observe and record if there are signs and symptoms of hypothermia and hyperthermia. -Adjust the room temperature to the needs of the patient. -Teach the patient to avoid heat exhaustion and heat stroke.
Hygiene and care of the skin, mucous and fanera.	[1801] Help with self-care: bathing/hygiene	-Control the skin integrity of the patient. -Maintain hygienic rituals. -Facilitate the maintenance of the patient's routines at bedtime, signs of sleep onset and familiar objects (for children their favorite blanket or toy, rocking, pacifier or story; for adults read a book or have a pillow from home), as appropriate. -Encourage the participation of parents/family in the usual rituals at bedtime, if applicable. -Provide help until the patient is fully capable of self-care.
Safety Maintenance of the Environment	[1805] Help with self-care: IADL	-Determine the individual's need for help with instrumental activities of daily living (e.g., shopping, cooking, housework, laundry, using public transportation, managing money, managing medications, communicating, and time management)). -Determine needs for changes related to safety in the home (e.g., widen door frames to allow wheelchair access to bathroom, remove rugs). -Determine home improvement needs to counteract disabilities (e.g., put large numbers on phone, turn up phone ring volume, move washer and other appliances to main floor, put side rails on hallway, grab bars in bathrooms).

Appendix C Collaboration Problems

Collaboration Problems			
PROFESSION	**OBSERVATIONS**	**NIC**	**ACTIVITIES**
Medicine	The medical implication is indisputable for the approach of this syndrome. The medical vision provides the necessary perspective for multidisciplinary treatment. The phenotype and the variable symptoms of the pathology require a medical study by different specialties and subsequently a pooling to achieve a complete medical assessment. The prescription and analysis of diagnostic tests, treatment and possible surgical interventions derived from the disease process are the main collaborative links with this healthcare group.	[2300] Medication administration [2395] Medication control. [2900] Surgical assistance. [7320] Case management. [7610] Diagnostic tests at the point of care. [7680] Help in exploration. [7690] Interpretation of laboratory data. [8020] Multidisciplinary care meeting	-Follow the five rules of proper medication administration. -Predict and provide the necessary supplies and instruments during the procedure. -Ensure that appropriate instruments, supplies, and equipment are sterile and in good working order. -Develop relationships with the patient, family, and other healthcare providers, as needed. -Use effective communication skills with the patient, family and other health care providers. -Record the results of the tests, in accordance with the institutional procedure. -Verify the results of the analytics performed at the point of care with a central laboratory when a critical clinical decision is to be made. -Inform the doctor about abnormal or critical results, as appropriate. -Explain to the patient each step of the procedure. Monitor the patient's condition during the procedure. Provide emotional support to the patient, if indicated. -Facilitate communication and collaboration between members of the multidisciplinary team to ensure effective and focused discussions that allow team members to solve problems and efficiently provide patient needs.
Psychology	Patients diagnosed with this syndrome are associated with a great psychological burden due to the setting in which the pathology develops. The uncertainty about the future, the lack of knowledge of their disease, the delay in diagnosis, the lack of effective treatment and the high invalidating, degenerative and dependent potential generate mental disorders that require psychological care. Anxiety, stress and depression are the most frequent mental disorders derived from this disease.	[5395] Improved self-confidence [5400] Enhancement of self-esteem. [5820] Decreased anxiety. [5270] Emotional support. [5450] Group therapy	-Encourage the patient to identify their strengths. Help the patient find self- acceptance. -Determine if the child/dependent adult is viewed differently by an adult based on sex, appearance, or behavior. -Identify crisis situations that may trigger abuse, such as poverty, unemployment, divorce or death of a loved one. -Listen carefully. -Reinforce the behavior, as appropriate. -Create an environment that facilitates trust. -Encourage the manifestation of feelings, perceptions and fears. -Identify changes in the level of anxiety. -Establish recreational activities aimed at reducing tensions. -Help the patient to identify situations that precipitate anxiety. -Choose group members who are willing to actively participate and take responsibility for their own problems. -Determine if the level of motivation is high enough to benefit from group therapy.
Physiotherapy	musculoskeletal involvement and its impact on the mobility of these patients requires rehabilitation care. Maintaining muscle tone, caring for joints, pain, and respiratory physiotherapy are key in caring for this syndrome.	[0200] Promotion of exercise [0201] Exercise promotion: strength training [0202] Promotion of exercise: stretching [0221] Exercise therapy: ambulation [0222] Exercise therapy: balance [0224] Exercise therapy: joint mobility [0226] Exercise therapy: muscle control	-Assist the patient with the initial ambulation, if necessary. -Instruct the patient/caregiver about safe transfer and ambulation techniques. -Control gait, balance and fatigue when walking. -Determine the limitations of joint movement and its effect on function. -Protect the patient from trauma during exercise. -Consult with the physical therapist about the ambulation plan, if necessary.

Collaboration Problems			
PROFESSION	OBSERVATIONS	NIC	ACTIVITIES
Chiropody	Acroosteolysis of the distal phalanges of the feet and hands with their corresponding deformity. Shortened and thick fingers and watch glass nails require specific care for this health group.	[1660] Foot care [1680] Nail care. [0221] Exercise therapy: ambulation	-Inspect if there is irritation, cracks, lesions, calluses, deformities or edema in the feet. -Inspect the patient's shoes to see if they fit correctly. -Soak your feet, if necessary. -Carefully dry the interdigital spaces. -Apply lotion. -Clean nails. -Apply/provide an assistive device (cane, crutches, or wheelchair, etc.) for ambulation if the patient is unstable. -Assist the patient with the initial ambulation, if necessary. -Instruct the patient/caregiver about safe transfer and ambulation techniques.

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DISCUSIÓN

Las enfermedades raras son un tema de investigación en apogeo en los últimos años, evidenciado por el aumento de las publicaciones científicas realizadas. A pesar de ello, aún es un campo que precisa de más estudios.

Atendiendo al abordaje clínico de este tipo de enfermedades, no cabe duda que el ideal sería uno multidisciplinar [1]. Un abordaje multidisciplinar en el que un mismo paciente sea valorado y tratado en conjunto por todas las profesiones sanitarias y no sanitarias que necesite. De esta forma, se adquiriría una visión completa del estado del paciente. Así lo corroboran varios estudios, entre los que destaca el de Hendriksz et al. En cualquier caso el paciente, el entorno y la familia son factores importantes a tener en cuenta en el desarrollo del abordaje y seguimiento de estos casos [2].

En el caso del Síndrome de Hajdu-Cheney, no existe un tratamiento curativo ni eficaz [3], cobrando vital importancia los cuidados de enfermería para el mantenimiento de la calidad de vida y el bienestar del paciente, su familia y entorno. No existe ninguna referencia científica sobre los cuidados de enfermería en el paciente diagnosticado del síndrome de Hajdu-Cheney, por lo que el plan de cuidados estándar específico para esta patología, presentado en este trabajo, actualizaría el conocimiento sobre este campo, repercutirá en la mejora de la calidad asistencial sanitaria facilitando el abordaje de la enfermedad, y en la calidad de vida de pacientes y familias [4].

La cronicidad [5], el carácter degenerativo[6] y alto potencial discapacitante descrito en este tipo de patologías, se observa con claridad en el reporte de los casos expuestos en este trabajo [7,8].

Uno de los aspectos que se encuentran como problemáticos y obstaculizantes en este campo, es el retraso del diagnóstico [9]. Atendiendo a los tiempos medios de diagnóstico, se observa la magnitud del problema [10]. En la mayoría de los casos la orientación al diagnóstico se realiza mediante la observación del fenotipo y la clínica presentada por el paciente y los hallazgos radiológicos encontrados [11]. Aunque el diagnóstico definitivo debe ser mediante confirmación genética [12] siempre y cuando la enfermedad sea de origen genético como el 80% de este tipo de enfermedades minoritarias.

Realizar un diagnóstico precoz y seguro en el Síndrome de Hajdu-Cheney es complicado. Estudios como el de Shawo et al. [13] revelan que la apariencia física y las pruebas radiológicas van a determinar la orientación del diagnóstico, aunque finalmente este debe ser mediante confirmación genética. Kawamura et al. [14] en su estudio nos indica la importancia de realizar una resonancia magnética como prueba complementaria a la exploración física. Cabe destacar el

estudio sobre capilaroscopia de Damian et al. [15] que propone esta prueba clínica para el diagnóstico.

Existen estudios de diagnóstico diferencial con este síndrome ya que a la hora de establecer un diagnóstico pueden aparecer similitudes con otras patologías. Sawin et al. [16] establecía en su estudio que la invaginación basilar no era solo un signo de HCS. Singh et al. [17] describía en su estudio las similitudes entre el síndrome de Hajdu-Cheney y los síndromes acroosteolíticos. Gripp en 2011 y Gripp et al. en 2015 [18,19] explicaban que el meningocele lateral a pesar de sus nexos clínicos con este síndrome no era la misma patología. O'Reilly et al. [11] señalan a la esclerodermia y la sarcoidosis como patologías que también cursan con acroosteolísis y por tanto la importancia de realizar un buen diagnóstico diferencial con ambas. Otro estudio reseñable sobre diagnóstico diferencial es el de Albano et al. [20] ya que establece las diferencias entre el síndrome de peroné serpentino, Melnick Needles y el propio síndrome de Hajdu-Cheney.

En los casos diagnosticados del Síndrome de Hajdu-Cheney descritos en este trabajo, se observa que aunque ambos se enfrentaron a una fase diagnóstica complicada, la mujer de 54 años [7] obtuvo su diagnóstico tras años de espera, sin embargo el caso del niño de 11 años [8] lo obtuvo superando los tiempos medios. Este hecho repercute notablemente en el desarrollo de la enfermedad y su evolución, como se presenta en los informes.

Los aspectos psicoemocionales de este tipo de pacientes son otro de los puntos clave a tener en cuenta para el abordaje clínico de estas patologías [21,22]. Estudios evidencian que ante la incertidumbre sobre el estado de salud y el futuro los niveles de ansiedad y depresión aumentan [23].

La existencia de tratamientos eficaces se hace esencial y para la mayoría de estas patologías no existe. Sin embargo, los indudables avances en la terapia génica tendrán un impacto positivo en el desarrollo de estas enfermedades, siendo una línea de tratamiento en el futuro [24].

En la búsqueda de un tratamiento eficaz podemos hablar de dos grandes vertientes, la farmacológica y la quirúrgica.

Existen estudios sobre tratamientos farmacológicos tan relevantes como los de Sakka et al. [25], Pittaway et al. [26] y James et al. [27] que trabajaron con biosfonatos. Para tratar los niveles de calcio, Adami et al. [28] probaron con denosumab, mientras que Tsinopoulou et al. [29] y Al-Mayouf et al. [30] lo hicieron con pamidronate. Hwang et al. [31] intentaron retardar el proceso de degradación ósea con el efecto del ácido zoledronico y McKiernan en 2008 y 2007 [32,33] realizaron un estudio farmacológico para tratar la osteoporosis.

Analizando la vertiente quirúrgica encontramos estudios que versan sobre el tratamiento de las complicaciones de este síndrome como la deformidad cifótica cervical en pacientes con osteoporosis de Mattei et al. [34], las restauraciones dentales de Vingerhoedt et al. [35] y Liljeström et al. [36], la reconstrucción espinal de Murtagh-Schaffer et al. [37] u otras intervenciones como la de translación de radio de Fujioka et al. [38] y Orneti et al. [39] que fueron capaces de tratar un colapso medular con tratamiento quirúrgico. Cabe destacar los estudios de Yamaguchi et al. [40] y August et al. [41] sobre anestesia y las indicaciones específicas para tratar a un paciente diagnósticado del síndrome de Hajdu-Cheney antes de ser intervenido y los de Zietz et al. [42] en analgesia post-quirúrgica para controlar el dolor.

A pesar de todos estos avances, los resultados de los estudios examinados en esta área nos indican que no existe aún un tratamiento curativo para esta enfermedad.

Cabe destacar como tratamiento pionero en este tipo de pacientes la terapia de vibración focal. Consistente en la aplicación de un tipo de vibraciones mecánicas mediante un aparato de vibración específico a nivel superficial sobre tendones o músculos. La mejora de la marcha y el mantenimiento del sistema muculoesqulético se hace evidente al tratar con esta terapia, tal y como se muestra en el caso pediátrico descrito en esta tesis.

Otra terapia para el mantenimiento de la musculatura en este tipo de pacientes es la hipoterapia, terapia con caballos. Los resultados son positivos al tratar a pacientes diagnosticados con parálisis cerebral.

Observando el panorama científico-clínico donde se desarrolla HCS cabe destacar que la estandarización y universalización en la valoración y la realización de pruebas diagnósticas facilitarían el flujo y el progreso en el mundo de la investigación. Una descripción de casos detallada mejoraría los tiempos de diagnóstico, elevando la calidad en el tratamiento y ofreciendo una mejor asistencia global a cada paciente.

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LIMITACIONES

Las limitaciones de este trabajo están íntimamente relacionadas con los principales problemas que presenta el campo de las enfermedades raras.

El escaso conocimiento existente sobre la enfermedad se hace evidente al cuantificar publicaciones en la literatura científica realizadas. Este hecho repercute negativamente en la realización de este trabajo, de la misma forma que la escasez de casos diagnosticados descritos.

La baja prevalencia, la dispersión geográfica y el lapsus de tiempo entre los casos documentados, además del seguimiento clínico prácticamente inexistente también limitan la actualización del conocimiento sobre el síndrome y dificulta la reunión y conformación de una muestra de estudio con garantías de evidencia.

Otra de las limitaciones que hemos observado es que aunque hay un apogeo en la investigación sobre enfermedades raras, no va acompañado de ayudas a la investigación, esto puede repercutir negativamente en dicha investigación por el coste que tiene que no pueda ser sufragado por los grupos de investigación.

LINEAS DE INVESTIGACIÓN FUTURAS

Fruto de esta tesis, se ha creado una línea de investigación específica para estudiar enfermedades raras, dentro del Grupo de Investigación CTS-1068 I-TranSalud, perteneciente a la Universidad de Granada. Esta línea de investigación pretende seguir con las líneas de acción propuestas por IRDiRC, EUCERD y el Plan de Atención a personas afectadas por Enfermedades Raras elaborado por la Consejería de Salud de la Junta de Andalucía.

Es un grupo que ya cuenta con expertos en la materia de nivel nacional y se presenta en expansión. A pesar de su reciente nacimiento ya cuenta con varias publicaciones sobre este tema.

- Martín-Martín, M.; Cortés-Martín, J.; Tovar-Gálvez, M.I.; Sánchez-García, J.C.; Díaz-Rodríguez, L.; Rodríguez-Blanque, R. Ehlers–Danlos Syndrome Type Arthrochalasia: A Systematic Review. *Int. J. Environ. Res. Public Health* **2022**, 19, doi:10.3390/ijerph19031870.

- Menor-rodríguez, M.J.; Martín, M.S.; Sánchez-garcía, J.C.; Montiel-troya, M.; Cortés-martín, J.; Rodríguez-blanque, R. Role and effects of hippotherapy in the treatment of children with cerebral palsy: A systematic review of the literature. *J. Clin. Med.* **2021**, 10, doi:10.3390/jcm10122589.

- Cortés-Martín, J.; López Peñuela, N.; Sánchez-García, J.C.; Montiel-Troya, M.; Díaz-Rodríguez, L.; Rodriguez-Blanque, R. Deletion Syndrome 22q11 . 2 : A Systematic Review. *Children.* **2022**, 9, 1–13.

Al mismo tiempo, se está trabajando en diferentes líneas de investigación que abrirán puertas de nuevo conocimiento.

- Embarazo, parto, puerperio, lactancia materna y sexualidad en pacientes con Ehlers-Danlos.
- Estudio sobre el Rol del Cuidador en pacientes con enfermedades raras.
- Calidad de vida en el Síndrome de Rett.
- Estudio del nivel de conocimiento actual sobre el mundo de las enfermedades raras en diferentes grupos poblacionales.

En cualquier caso, las inquietudes por el Síndrome de Hajdu-Cheney persisten y se seguirán estudiando diferentes vertientes de la línea trazada.

CONCLUSIÓN

El avance de la investigación en el campo de las enfermedades raras es indudable en los últimos años. A pesar de esto, aún quedan muchas vertientes por explorar.

La búsqueda de un tratamiento eficaz para cada enfermedad es la principal preocupación de la mayoría de los estudios, pero no se deben desatender otros aspectos como la descripción fenotípica completa, las descripciones de casos, el fomento del registro de pacientes en bases de datos oficiales, el tratamiento de los aspectos psicoemocionales de los pacientes y las familias y el mantenimiento de la calidad de vida.

El abordaje clínico, debe ser en cualquier caso, de carácter multidisciplinar y siempre teniendo en cuenta al paciente, su familia y su entorno.

En concreto, el Síndrome de Hajdu-Cheney atiende a tres grandes características; la variabilidad fenotípica, el carácter degenerativo y un cuadro de osteolísis de las falanges distales y osteoporosis generalizada acompañado de otras manifestaciones clínicas.

Se hace preciso una descripción completa del fenotipo de la enfermedad atendiendo a esa posible variabilidad de expresión genética, ya que este aspecto mejorará los tiempos de diagnóstico.

El mantenimiento de la calidad de vida de estos pacientes se hace crucial, ya que no existe un tratamiento eficaz. Los cuidados de enfermería y la colaboración con otras profesiones sanitarias adquieren un rol importante en este tema.

Terapias como la vibración focal, pionera en este campo, debe ser la terapia de elección para la mejora de la marcha y el mantenimiento del sistema musculoesquelético, debido a sus resultados positivos.

La difusión y la visibilización de proyectos relacionados con las enfermedades raras son dos aspectos de gran interés que favorecen el acceso a la información referente a este campo.

A pesar de todos los avances para este síndrome expuestos en este documento, sigue siendo necesario el avance de la investigación para esta enfermedad con estudios de mayor envergadura.

ANEXOS

DICTAMEN ÚNICO EN LA COMUNIDAD AUTÓNOMA DE ANDALUCÍA

D/Dª: ANTONIO SALMERON GARCIA como secretario/a del CEIM/CEI Provincial de Granada

CERTIFICA

Que este Comité ha evaluado la propuesta del promotor/investigador (No hay promotor/a asociado/a) para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	ESTUDIO EPIDEMIOLÓGICO Y ABORDAJE INTEGRAL DE LA ENFERMEDAD DE HAJDU-CHENEY
Protocolo, Versión:	v3
HIP, Versión:	v3
CI, Versión:	v3

Y que considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y se ajusta a los principios éticos aplicables a este tipo de estudios.

La capacidad del/de la investigador/a y los medios disponibles son apropiados para llevar a cabo el estudio.

Están justificados los riesgos y molestias previsibles para los participantes.

Que los aspectos económicos involucrados en el proyecto, no interfieren con respecto a los postulados éticos.

Y que este Comité considera, que dicho estudio puede ser realizado en los Centros de la Comunidad Autónoma de Andalucía que se relacionan, para lo cual corresponde a la Dirección del Centro correspondiente determinar si la capacidad y los medios disponibles son apropiados para llevar a cabo el estudio.

Lo que firmo en Granada a 02/03/2021

D/Dª. ANTONIO SALMERON GARCIA, como Secretario/a del CEIM/CEI Provincial de Granada

CERTIFICA

Que este Comité ha ponderado y evaluado en sesión celebrada el 23/02/2021 y recogida en acta 2/21 la propuesta del/de la Promotor/a (No hay promotor/a asociado/a), para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	ESTUDIO EPIDEMIOLÓGICO Y ABORDAJE INTEGRAL DE LA ENFERMEDAD DE HAJDU-CHENEY
Protocolo, Versión:	v3
HIP, Versión:	v3
CI, Versión:	v3

Que a dicha sesión asistieron los siguientes integrantes del Comité:

Presidente/a

D/Dª. AURORA BUENO CAVANILLAS

Vicepresidente/a

D/Dª. Paloma Muñoz de Rueda

Secretario/a

D/Dª. ANTONIO SALMERON GARCIA

Vocales

D/Dª. PATRICIA GALVEZ MARTIN
D/Dª. Francisco Manuel Luque Martínez
D/Dª. Juan Ramón Delgado Pérez
D/Dª. Berta Gorlat Sánchez
D/Dª. José Dario Sánchez López
D/Dª. Sonia Dominguez Almendros
D/Dª. Juan Mozas Moreno
D/Dª. SALVADOR ARIAS SANTIAGO
D/Dª. MARIA ESPERANZA DEL POZO GAVILAN
D/Dª. Francisco OValle Ravassa
D/Dª. ANTONIO MORALES ROMERO
D/Dª. MARTA CUADROS CELORRIO
D/Dª. MARIA ANGELES GARCIA LIROLA
D/Dª. Encarnación Martínez García
D/Dª. FRANCISCO LUIS MANZANO MANZANO
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D/Dª. ANGEL COBOS VARGAS
D/Dª. LUIS MIGUEL DOMENECH GIL
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D/Dª. Luis Javier Martínez González
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D/Dª. MARÍA DOLORES GARCÍA VALVERDE
D/Dª. ESTHER MOLINA RIVAS
D/Dª. ANTONIO JUAN PÉREZ FERNÁNDEZ

D/Dª. JUAN CARLOS NAVARRO BARRIOS
D/Dª. ANTONIO JIMENEZ PACHECO

Que dicho Comité, está constituido y actua de acuerdo con la normativa vigente y las directrices de la Conferencia Internacional de Buena Práctica Clínica.

Lo que firmo en Granada a 02/03/2021