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Research

Congenital chloride diarrhoea: a new genetic mutation

AM Campos Martínez[1] (anacampos30 at hotmail dot com), A Abril Molina[1], R Martínez de la Ossa Sáenz-López[1], P Azcón González de Aguilar[1], M Martínez Atienza[2], C González Hervás[1], J Maldonado Lozano[3], E Ocete Hita[1]
[1] Pediatric Intensive Care Unit. Virgen de las Nieves Hospital. Granada. Spain. [2] Genetics. Virgen de las Nieves Hospital. Granada. Spain. [3] Pediatrics. Virgen de las Nieves Hospital. Granada. Spain

DOI //dx.doi.org/10.13070/rs.en.1.830
Date 2014-05-25
Cite as Research 2014;1:830

Abstract

Congenital chloride diarrhoea is an autosomal recessive disease associated with the mutation of the SLC26A3 gene on chromosome 7q31.1. It consists of an alteration in the chloride-bicarbonate exchanger in the intestine, starting in prenatal life, and causing persistent secretory diarrhoea practically from birth. We present a typical clinical case of the disease, with a history of polyhydramnios and prematurity, early presentation, occurring at one month of life, and which was difficult to control despite high levels of sodium chloride and potassium chloride administered following clinical diagnosis of the disease. The present study describes a genetic study that revealed a previously unreported mutation of the disease. The genetic study showed heterozygosity for the nucleotide changes in the SLC26A3 gene: c.1591 dup (p.Glu531Glyfs*23) and c.1696C>T p.(Arg566*). In the genetic study of the parents, the father was found to be a heterozygous carrier of the change c.1696C>T (p.Arg566*) in the SCL26A3 gene, and the mother was a heterozygous carrier of the mutation c.1591dup (p.Glu531Glyfs*23) in the same gene. The description of previously undescribed genetic mutations of diseases such as congenital chloride diarrhoea is of vital importance for early diagnosis, especially when the clinical diagnosis is unclear.

INTRODUCTION

Congenital chloride diarrhoea is one of the most common causes of severe congenital diarrhoea. To date, its origin has been ascribed to an autosomal recessive disorder associated with a mutation of the SLC26A3 gene on chromosome 7q31.1, which encodes the transporter of the sodium-independent chloride-bicarbonate intestinal exchanger [1].

We describe a compatible clinical and biochemical case, of early presentation, without the above-mentioned mutation, but with mutations associated with that gene.

CLINICAL CASE

Male aged 3 months, admitted with moderate dehydration and severe metabolic alkalosis.

Family history: Mediterranean-European parents, not consanguineous, no relevant pathologies. Mother of below-average height, gestational diabetes controlled with insulin. Healthy brother, aged 2 years.

Personal background: Premature birth at 33 weeks, weight 2.4 kg, with polyhydramnios and possible prenatal intestinal obstruction. Remained hospitalised for 11 days after birth. Passage of meconium in the first 24 hours with good intestinal transit, lumpy stools, no feeding problems. Opaque enema revealed dilated colon and normal blood gases. Weight at discharge from hospital: 2.7 kg.

At a month and a half of life, difficulty in feeding began, with rejection, frequent bowel movements (in the parents' opinion, this was not alarming), failure to thrive, irritability, and various unsuccessful changes in feeding patterns.

Patient admitted as an emergency case following a worsening of symptoms, with moderate general status, moderate dehydration, abdominal distension with visible bowel loops but no visceromegaly, normal temperature, no other significant findings. Weight 3.5 kg. Blood analysis results: pH 7.7, pCO2 30.5 mmHg, hydrogen ions 20nmol /L, HCO3 40 mmol /L, base excess 15.9 mmol/L, sodium 126meq /L, potassium 3.1 mEq/L, chlorine 77meq /L, lactate 7.5 mmol /L. Urine pH 6.8, hydrogen ions 155nmol /L, sodium 28meq /L, potassium 17meq /L, chlorine 2meq /L.

Intravenous rehydration was initiated without incident, and it was observed that even during the diet period, watery stools were passed frequently; accordingly, stool gas analysis was performed, producing the following results: pH 6.09, sodium 90meq/L, potassium 45.6 mEq/L, chlorine 133meq/L. The remaining biochemical controls, hepatorenal profile and microbiological studies were negative.

Other causes of metabolic alkalosis, such as cystic fibrosis and Bartter syndrome, were rejected.

After intravenous electrolyte correction of sodium, potassium and chlorine, clinical improvement was obtained, with adequate oral intake. Oral intake of potassium chloride, sodium chloride and omeprazole was maintained. The patient was discharged with normal oral feeding and supplements of NaCl (2.7 meq/kg/day) and ClK (1.5 meq/kg/day), subsequently adjusted according to need.

In the follow-up, several relapses occurred, coinciding with intercurrent infections. A genetic study revealed heterozygous nucleotide changes in the SLC26A3 gene: c.1591 dup (p.Glu531Glyfs*23) and c.1696C>T p. (Arg566*), a mutation that has not been reported previously. This genetic study was conducted in a specialised genetics laboratory, using PCR amplification of the fragments corresponding to the coding region and to flanking areas of the SLC26A3 gene, with subsequent sequencing of the fragments obtained. In the genetic study of the subject's parents, the father was found to be a heterozygous carrier of the change c.1696C>T (p.Arg566*) in the SCL26A3 gene, and the mother was a heterozygous carrier of the mutation c.1591dup (p.Glu531Glyfs*23) in the same gene. Therefore, as both parents were heterozygous carriers, the risk of transmission was 25% affected, 50% healthy carriers and 25% healthy non-carriers.

DISCUSSION

Congenital chloride diarrhoea was described in 1945 by Gamble and Darrow. It is currently considered an autosomal recessive disease, associated with mutation of the SCL 26A3 gene that encodes the transporter of the sodium-independent chloride-bicarbonate intestinal exchanger [1]. The prevalence varies considerably, the condition being more common in Finland, Poland and Arab countries in the Persian Gulf [2]. It is classed as a rare disease in the OMIM database (# 214700) [1].

The Cl-/HCO3- exchanger absorbs the chlorine produced by gastric HCl and by CFTR, and secretes bicarbonate into the intestinal lumen, which neutralises the acidity of gastric acid secretion [1]. The alteration of this exchanger produces an acidification of the intestinal contents, chlorine loss in the faeces and metabolic alkalosis, which in turn produces a defect in the absorption of sodium by the Na+/H+ exchanger. Also associated with this pathology are hypokalaemia and increased aldosterone and renin activity [1] [3].

The natural history of the disease begins during pregnancy with the prenatal presence of polyhydramnios and dilated bowel loops, which may erroneously suggest intestinal obstruction, and this frequently leads to preterm delivery [1] [3] [4].

After birth, the main clinical signs are watery diarrhoea, abdominal distension and jaundice, which again suggests intestinal obstruction.

The initial management of children suffering from this disease is electrolyte replacement to correct the acid-base imbalance. Early in the neonatal period, and during decompensation, salt replacement should initially be intravenous, and later delivered orally. The dosage of chlorine necessary depends on the losses of each patient and must be adjusted to the individual case, although 6-8 mmol/kg/d is recommended for children and 3-4 mmol/kg/d for older patients [5]. As the genetic defect is permanent, subjects will continue to present diarrhoeal stools, but this will decrease with age. These patients may suffer decompensation due to intercurrent infections [5] (studies have reported benefits from the use of proton pump inhibitors [6] and butyrate [7], although their exact role remains unclear [8]), intestinal inflammation and inguinal hernias [5], kidney damage caused by the continuing compensation of electrolytes through the kidney [5], hyperuricaemia [5], impaired secretion from the sweat glands [5] and male infertility [5] [9]. Cholestyramine may be useful in reducing diarrhoea in decompensation, although its effect has been described as transient, lasting 2-4 weeks [10].

To adequately monitor these patients, it has been proposed that children aged under 3 years should be given quarterly growth controls, together with analyses of blood gases, serum electrolytes, creatinine and chloride in the urine; twice-yearly controls of renin activity and plasma aldosterone; and analyses of glomerular filtrate every 2-3 years [5]. To determine the appropriate dose of Cl, levels of chlorine in urine should be measured, taking as good therapeutic values 10-30 mmol/l in children aged 3-7 years and 30-50 mmol/l in older children [5].

We describe a new genetic mutation in the gene SLC 26A3: c.1591dup, (p.Glu531Glyfs*23), c.1696C>T (p.Arg566*), which accounts for this condition and should be taken into consideration when clinical and laboratory findings are compatible with this pathology.

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ISSN : 2334-1009