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Short report

Jejunal atresia and anterior chamber anomalies: Further delineation of the Strømme syndrome

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ABSTRACT

Strømme syndrome is a rare multiple congenital malformation syndrome consisting in apple peel intestinal atresia, ocular anomalies, microcephaly and developmental delay. To date, this condition was described in a couple of sibs and 7 additional sporadic patients. We report on a 11-month-old female, who requested surgical correction for jejunal atresia shortly after birth and also presented with megalocornea and persistence of the pupillary membrane. Microcephaly and developmental delay were absent at last examination. An oligonucleotide CGH-array analysis excluded cryptic chromosome rearrangement(s). Comparison of the previously published and present patients added some details on the natural history of Strømme syndrome. Delivery is usually performed preterm possibly due to polyhydramnios. Birth parameters, especially head circumference, are commonly at the lower end of the normal range. Microcephaly is more frequently but not constantly observed in older individuals, thus suggesting a progressive course, and may relate to an underlying neuronal migration defect. Jejunal atresia has an apple peel appearance in most but not all patients and its post-surgical course is usually uneventful. The ocular phenotype comprises a wide range of anterior chamber anomalies with sclerocornea/corneal leukoma being the most common.

1. Introduction

In 1993, Strømme et al. described two siblings with the previously unreported association of anterior chamber anomalies, "apple peel" type jejunal atresia and microcephaly (Strømme syndrome, SS; OMIM 243605) [7]. After a 4 year follow-up, one sib revealed subaverage mental capacity and the other mental retardation [6]. Subsequently, 6 sporadic patients were described with similar phenotypes [1–5,8]. An additional subject was reported showing apple peel intestinal atresia, facial dysmorphism, developmental delay and coloboma of the optic nerve, but lacking any anterior chamber anomaly [9].

Although the combination of eye and jejunal anomalies appeared a consistent phenotype, the associated clinical variability and etiology were poorly understood. Autosomal recessive mutation, variegated aneuploidy and vascular disruption were proposed as possible causes in single reports [2,4,7]. Several genes involved in isolated and syndromic forms of anterior chamber anomalies were screened in a single subject and resulted negative [8].

Here, we report on a 1-year-old girl with bilateral megalocornea, persistence of the pupillary membrane and apple peel intestinal atresia. The absence of developmental delay and microcephaly in our patient was of interest for delineating the core phenotype and natural history of SS. Negative CGH microarray analysis pointed out a non-chromosomal origin of SS in this case.

2. Clinical report

The proband was a 11-month-old Caucasian girl born to a 15-year-old mother and her 23-year-old unrelated husband. Family history was unremarkable especially for developmental disabilities, eye anomalies and malformations. Pregnancy screening for rubella, cytomegalovirus and toxoplasma was negative. There was no history of preeclampsia and gestational diabetes. Pregnancy was complicated by polyhydramnios which first appeared at 30 weeks of

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gestation. Delivery was then performed by Cesarean section at 36 weeks. Birth weight was 2.140 g (10th centile) and Apgar score $6^1/8^5/9^{10}$, while head circumference and length were unknown. Anterior fontanel was 1 cm × 1 cm. Shortly after birth, she presented with bilious vomiting and a plain abdominal radiograph was indicative for upper intestinal obstruction. Then, she was subjected to laparotomy which disclosed intestinal malrotation with multiple jejunal constrictions and a coiled-like ("apple peel") appearance of the upper intestinal tract (Fig. 1a). A second intervention was requested 20 days afterwards for post-surgical adhesions. Recovery evolved uneventful and the patient was discharged after a few days.

At 4 months of age, during an outpatient routine visit at the clinical genetics service of our Institution, increased corneal diameter and a white dot at the center of the pupil were noted on both eyes. An ophthalmological survey demonstrated corneal diameter of 13 mm on the right and 13.5 mm on the left, and persistence of the pupillary membrane of Wakendorf on both eyes (Fig. 1b). Corneal diameters indicated bilateral megalocornea (mean corneal diameter in infants = 10 mm; megalocornea = corneal diameter >12 mm). Anterior chamber and fundus oculi examination, eye ultrasound and visual evoked potentials were unremarkable. Persistence of the pupillary membrane was surgically treated. A post-surgical evaluation noted residual myopia and right esotropia. Eye pressure remained always within normal limits. The patient sat unsupported at 8 months of age, crawled at 9 months and said first words at 9.5 months. The first teeth erupted at 8 months. Heart and abdominal ultrasound were unremarkable.

At last examination (11 months of age), patient's height was 9.200 g (25–50th centile), length 74 cm (50th centile) and head circumference 45 cm (9th centile). She still did not walk alone but, considering prematurity, displayed normal psychomotor development and socialized appropriately for age. She was able to grasp objects and brings them to her eyes. On physical examination, the patient exhibited bilateral megalocornea, right esotropia and blue sclera (Fig. 1c). No additional dysmorphism was evident. Due to the apparently normal psychomotor development, absence of microcephaly or any focal deficit, parents decided to do not perform brain magnetic resonance. Peripheral blood karyotype on 50 metaphases was normal female. In order to investigate genomic cryptic rearrangements, a CGH-Array analysis was performed using the Agilent Human Genome CGH Microarray 44K (43KB overall median probe spatial resolution and 24KB median probe spacing in Refseq genes). Statistical analysis was performed by CGHweb with a cutoff threshold equal to 0.2. The CGH analysis did not find any statistical significant aberrant region.

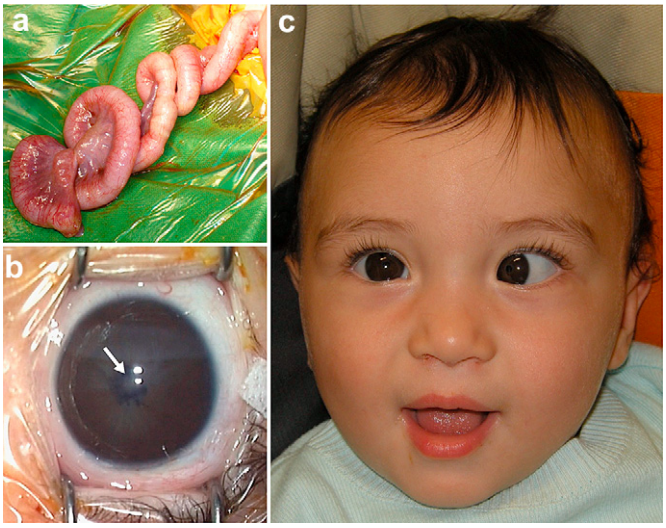

Fig. 1. Intraoperatory image. Note "apple peel" appearance of the removed intestinal segment. (b) Increased corneal diameter and persistence of the pupillary membrane presenting as a central white dot (arrow). (c) Facial features. Note absence of any significant dysmorphism except for megalocornea and left esotropia.

3. Discussion

In our patient, the unusual combination of apple peel intestinal atresia and multiple eye anomalies was consistent with SS. In contrast with many previously published SS patients, the present case showed neither microcephaly or developmental delay. In addition, the ocular phenotype appeared unusual compared to the original description [7]. In order to better define the SS phenotype and its natural history, we compared our findings with those reported in the 9 previously published patients (Table 1) [1–9].

Based on the present case and literature review, preterm delivery was registered in most individuals (8/10) and in at least 2 of them this was caused by polyhydramnios secondary to intestinal atresia. Birth weight (7/10) and length (5/6) were frequently at or below the 25th centile corrected for gestational age and this trend remained valid also in the postnatal life. Although head circumference was often below the 25th centile, a head circumference below the 3rd centile was reported in 3 cases only [1,3,5]. Conversely, true microcephaly became more evident in subsequent observations, thus presenting as a progressive feature at least in some cases. In according to this impression, the patients by Strømme et al. [7] and van Bever et al. [8] displayed a nearly normal birth head circumference, which fell below the 3rd centile afterwards. Also in the present patient, the disproportion of height and head circumference measurements at 11 months could predict a similar trend.

Developmental delay was manifested in 2/3 of the patients. The degree of developmental delay was variable, ranging from mild [6] to moderate-severe mental retardation [4,5]. Of note, the 3 subjects, including the present case, who lacked cognitive impairment were aged below 1 year and, in the two original patients, cognitive underdevelopment was noted in late infancy [7]. Therefore, it could be speculated that the onset of developmental delay may be age related and possibly coupled with progressive microcephaly. Of interest, brain magnetic resonance imaging or computer tomography was performed in 6 patients [1,3–6] and resulted positive in 3. Abnormal gyration and neuronal migration may represent the primary defect underlying poor head circumference achievement in at least 2 patients [3,4]. This finding could be underestimated depending on the accuracy of neuroradiological evaluation and being jeopardized by possible concurrent central nervous system malformations, such as hydrocephalus [5].

The SS core phenotype is composed of intestinal atresia and ocular anomalies. The former always affected the jejunum and usually in form of apple peel intestinal atresia. However, in 2 subjects this peculiar presentation was not registered [3,4]. Consequently, we propose to substitute the term "apple peel intestinal atresia" with "jejunal atresia" in the definition of the syndrome. The surgical outcome of intestinal atresia in SS is good, as early death occurred in one subject only [5]. Eye involvement was extremely variable but quite constantly affected the anterior chamber. The most common eye features included sclerocornea/corneal leukoma (7/11), shallow anterior chamber (3/11), iridocorneal synechiae (3/11) and corectopia (3/11). Rarer anterior chamber findings were microcornea (with or without microphthalmia), megalocornea, descematocoele and persistence of the pupillary membrane. The work by Waters and colleagues suggested that anterior chamber anomalies may be absent and that the ocular phenotype could be limited (or extended) to optic nerve malformation [9]. However, whether or not this patient belongs to SS is still debated [8]. As ocular features in SS may be very mild and