Spectrum of renal abnormalities in ATR-X syndrome: a case report of 2 twins


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Abstract

ATR-X syndrome is an X-linked mental retardation syndrome characterized by mental retardation, alpha thalassaemia and distinct facial features which include microcephaly, frontal hair upsweep, epicanthic folds, small triangular nose, midface hypoplasia and carp-shaped mouth. Here we report two twins with this syndrome.

Keywords: alpha-thalassaemia, ATR-X, developmental delay, X-inactivation

Introduction

X-linked alpha thalassaemia mental retardation (ATR-X) syndrome is a recessive X-linked disease that, in males, is associated with profound developmental delay, facial dysmorphism, genital/urinary abnormalities and alpha thalassaemia. Female carriers are usually physically and intellectually normal. We describe the case of 2 male twins with ATR-X syndrome.

Case 1

Giuseppe was born in the thirty-fifth week of gestation from twin pregnancy complicated by threat of abortion in the first trimester and by threat of premature birth in the 3th trimester. Birth weight 2.940 Kg. In the first days of life, he needed CPAP for respiratory distress.

In the year 2003, for the detection of generalised hypotonia and development delay with difficulty feeding, he went to our hospital, where was diagnosed ATR-X syndrome. In 2005 he underwent a Nissen fundoplication surgery for severe gastroesophageal reflux. In 2006, he underwent surgery for bilateral cryptorchidism. He is also affected by ultrashort Hirschsprung’s disease. In 2010, he arrived in our nephrology word for abdominal pain, with laboratory and ultrasonographic diagnosis of renal stones and crystalluria.

Case 2

Francesco was born in the thirty-fifth week of gestation from twin pregnancy complicated by threat of abortion in the first trimester and by threat of premature birth in the 3th trimester. Birth weight 2.480 Kg. From the first days of life, he had generalised hypotonia and development delay with difficulty feeding. ATR-X syndrome was diagnosed in 2003 at the Gaslini hospital in Genoa. In 2005 he underwent a Nissen fundoplication surgery for severe gastroesophageal reflux. In 2006, alterations of vertebral column were diagnosed by radiography, characterized by moderate right lumbar spine scoliosis; static pelvic obliquity and asymmetry of the profiles of the upper femoral heads; kyphosis and lumbar lordosis. In 2006, he underwent surgery for bilateral cryptorchidism. In 2009, he arrived in our nephrology word for recurrent urinary tract infections, with laboratory and ultrasonographic detection of microproteinuria and ultrasonographic detection of microlithiasis. The renal scintigraphy showed a slight alteration in the left kidney, expression of previous episodes of urinary infection. This finding, however, was not an expression of chronic scar damage. The microproteinuria, the concomitant alteration of urinary beta 2 microglobulin is expression of a tubular origin of the proteinuria.

Discussion

X-linked alpha thalassaemia mental retardation (ATR-X) syndrome is a recessive X-linked disease derived from mutations in the ATRX gene that encodes the widely expressed ATRX protein. The diagnosis can be established by detection of phenotypic characteristics, identification of ATRX gene mutations, ATRX protein studies and X-inactivation studies. There are few sine qua non diagnostic features (1). The 95% of cases have severe to profound mental retardation. In early childhood generalised hypotonia is common and all milestones are delayed. It’s typical a severe expressive language disorder. Most have no speech, although an increasing number of individuals are being identified who use a few words or signs. With age, affected individuals often develop a tendency toward spasticity. Seizures occur in approximately one third of cases and most frequently are clonic/tonic or myoclonic in nature. Sensorineural deafness and alpha thalassaemia were previously considered as features that distinguishes ATR-X syndrome from the allelic condition Juberg-Marsidi syndrome (2). The subjects are usually described by their parents as content and of a happy disposition. Affected individuals exhibit a wide range of emotions that are usually appropriate to their circumstances. There may be emotional fluctuation with sudden switches between almost manic-like excitement or agitation, and withdrawal and depression. In several instances, are described episodes of crying that have been thought to be associated with pain, possibly of a gastrointestinal origin. Distinctive facial traits are most readily recognised in early childhood and the gestalt is probably secondary to facial hypotonia (Fig. 1).
Genital abnormalities are seen in 80% of children. These may be very mild (e.g., undescended testes or deficient prepuce), but the spectrum of abnormality extends through hypospadias and micropenis to ambiguous female external genitalia. The most severely affected children, who are clinically defined as male pseudohermaphrodites, are usually raised as females.

A wide range of relatively mild skeletal abnormalities were noted, some of which were probably secondary to hypotonia and immobility (3). Fixed flexion deformities, particularly of the fingers, were common. Other abnormalities of the fingers and toes were also observed: clinodactyly, brachydactyly, tapering of the fingers, drum stick phalanges, overlapping of the digits, and foot deformities. Recurrent vomiting, regurgitation or gastro-oesophageal reflux, particularly in early childhood, are common findings. Excessive drooling is very common, as is frequent eructation. Constipation occurs often, and in some individuals is a major management problem. Martucciello et al. (4) demonstrated ultra-short Hirschsprung’s disease and colonic hypoganglionosis in two affected children. Evidence suggests that affected individuals are susceptible to peptic ulceration. Oesophagitis, oesophageal stricture and peptic ulcer have observed endoscopically in single cases. Pain resulting from peptic ulceration is one possible explanation for the episodes of persistent crying and food refusal reported by a number of parents. A wide range of cardiac abnormalities have been noted: septal defects, patent ductus arteriosus, pulmonary stenosis and aortic stenosis. Structural abnormalities of the kidneys and ureters are well described and may predispose individuals to urinary tract infections. Renal abnormalities as hydronephrosis, renal hypoplasia or agenesis, polycystic kidney and vesico-ureteric reflux may present with recurrent urinary tract infections, as it has been seen in the cases of our twins (Tab.1).

This syndrome results from mutations in the ATRX gene that encodes the widely expressed ATRX protein. ATRX mutations cause diverse changes in the pattern of DNA methylation at heterochromatic loci but it is not yet known whether this is responsible for the clinical phenotype. The gene involved in the disease, ATRX, lies at Xq13.3 (5). It spans about 300 kb of genomic DNA and contains 36 exons (6). It encodes at least two alternatively spliced ~10.5 kb mRNA transcripts which differ at their 5’ ends and are predicted to give rise to slightly different proteins of 265 and 280 kD respectively. A further transcript of ~7 kb represents an isoform which retains intron 11 and truncates at this point. This gives rise to a truncated protein isoform, ATRXt, which is conserved between mouse and man (7). The protein belongs to the SNF2 family of helicase/ATPases, members of which are involved in a wide variety of cellular functions including the regulation of transcription (SNF2 and MCT1), control of the cell cycle (NPS1), DNA repair (RAD16, RAD54 and ERCC6) and mitotic chromosome segregation (lodestar). It is believed that their function is to facilitate these processes by remodelling chromatin. The function of the ATRX protein is unknown, but the fact that alpha-globin expression is perturbed in the patients suggests that it may play a role in gene expression. Protein studies have shown that ATRX is a nuclear protein with a punctate staining pattern (8). Management of patients with ATR-X is based on a multidisciplinary approach focusing on developmental skills and secondary problems related to the syndrome. The presence of anaemia due to alpha-thalassaemia does not require any treatment in general (9).

In conclusion, this report described the presence of ATR-X syndrome in two twins displaying many of the typical features associated with this syndrome. This case is
unusual because both twins do not have alpha-thalassaemia and Francesco also has a tubular dysfunction, renal failure whose association with ATR-X has not yet been described in scientific literature. According to the broad spectrum of renal abnormalities, only Francesco has vesico-ureteric reflux, while both twins have kidney stones. Therefore, in the face of children with this syndrome is good investigate also the tubular function, in order to exclude a possible deficit.

References