Renal/urinary abnormalities (15%)

Only some of the children have a degree of bowel and bladder control. One of the commonest problems is "reflux", when on emptying the bladder some of the urine shoots back up towards the kidney. This may predispose to urinary tract infections. The urinary system should be imaged with ultrasound at diagnosis. Urine should be cultured when there are symptoms such as fever or pain on urination.

Digestive systems

Early feeding may be problematic due to poor sucking reflex and generalized floppiness. Swallowing may be rather uncoordinated. Frequent regurgitation of food or vomiting are common though this often improves as the child gets older. A few children have had episodes when the gut appears to have "gone on strike" and stopped the normal contractions that propel the contents along the length of the gut (an ileus). Constipation occurs often, and in some individuals is a major management problem. It may be associated with ultra-short Hirshsprung disease and colonic hypoganglionosis. Where ultra-short segment Hirshsprung disease is identified, the therapy of choice is sphinctero-myectomy if dilation of the internal sphincter proves ineffective.

Short Stature

Many of the children have short stature and their growth is consistently behind that of others of a similar age. In a few, growth is within the normal range in childhood but they fall behind during the growth spurt of the early teens.

Seizures (30%)

Seizures occur in approximately one third of cases and most frequently are clonic/tonic or myoclonic in nature. In the main, seizures respond well to standard therapy. Some affected individuals exhibit jerking movements which, though appearing to be seizures, are not associated with epileptiform activity on EEG.

Electroencephalogram may need to be carried out with video recording to correlate seizure activity and abnormal movements.

Vision and hearing

Refractive abnormalities, in particular myopia, are common and in some cases there may be high myopia (> -10 diopters). Strabismus may be present. Pale discs or optic atrophy are frequently observed. Rarely the individual may be blind. A formal ophthalmologic evaluation is appropriate at diagnosis and regularly thereafter.

Sensorineural deafness may be present (<10%). Standard distraction tests and, if suspected, auditory evoked responses should be done. Hearing loss should be managed as for any infant.

Life Expectation

Because the condition has not so long been recognised, the group of affected boys has not been sufficiently followed to know much about their life expectations. Pneumonia is frequently the cause of death. Repeated chest infections are possibly related to episodes of vomiting and food going down the 'wrong way' into the lungs.

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ATR-x Syndrome

information for physicians

The Dutch ATR-x SYNDROME Foundation

What is ATR-x Syndrome?

X-linked alpha thalassaemia mental retardation syndrome, or ATR-X syndrome for short, is one of many genetic conditions which affects males and is associated with profound developmental delay, a characteristic facial appearance, genital abnormalities and a type of anaemia called alpha thalassaemia. Females are often (about 75%) carriers of the ATR-X gene, but there are also families known where the mutation is arisen for the first time and the mother is not a carrier.

How does ATR-x Syndrome arise?

Mutations in the ATR-x gene at the moment are the only known cause of ATR-X syndrome.

There are many different sorts of mutations that affect this gene but the most common are missense mutations (80%) which are usually a single change in one of the bases making up the DNA sequence of the gene (like a spelling mistake involving a single letter). These mutations cause the protein which is encoded by the gene to be altered by a single building block – a single amino acid. Most of these changes make the protein more unstable so that the steady state levels of the ATRX protein in the cell are substantially reduced.

The mutations cluster in two parts of the gene which encode functional domains. One region is the ADD domain (ATR-x, DNMT3, DNMT3L). It comprises 4% of the protein but contains ~50% of the mutations. Most of the other mutations lie in the ATPase domain which powers this molecular motor. Mutations in the ADD domain have a somewhat more severe consequence than ATPase mutations namely less likely to have any speech and less likely to be walking by 10yrs but there is a lot of overlap in the associated development problems resulting from mutations in these two domains.

Two small subgroups also exist: one has a mutation near the beginning of the protein and is associated with a variable phenotype so some children have mild/moderate intellectual disability (ID) compared to the severe/profound intellectual disability seen with other children; another group with mutations at the end of the protein commonly (but not invariably) have severe genital abnormalities and several such children have been raised as girls.

How can ATR-x Syndrome be diagnosed?

The characteristic facial appearance in a child with severe developmental delay is the first clue to the diagnosis. The presence of alpha thalassaemia may help confirm the diagnosis. It is then relatively easy to search for a mutation in the ATR-X gene to identify the cause. DNA testing via Whole Exome Sequencing is the recommended method in the Netherlands.

What are the features of ATR-X syndrome?

Learning difficulties (96%)

In the majority of the children the learning difficulties are classified as severe. Speech is usually absent though some learn a few words and a small repertoire of Makaton signs. Some are restricted to recognition of the family and awareness of their surroundings, others understand more, such as learning where a biscuit tin is kept, learning to turn on the TV and obeying simple commands.

The "motor milestones", such as sitting unsupported or crawling, are delayed. About half of the children learn to walk: 45% learn to walk by the age of nine.

Characteristic facial appearances (90%)

Many syndromes, for example Downs, are associated with a recognisable facial appearance. This is true also of ATR-X syndrome, though the characteristic facial appearance is easier to recognise in early childhood. The head size is often small (microcephaly, 75%), the eyes widely spaced, the bridge of the nose rather broad and flat, the nose itself is small, triangular and upturned at the end. The upper lip has a tented appearance and the lower lip is full and everted.

Anaemia (α thalassaemia) (85%)

There are many causes of anaemia but in ATR-X it is due to a reduction in the manufacture of one of the proteins, α globin, that makes up haemoglobin. This form of anaemia is called α thalassaemia. α Thalassaemia can be diagnosed with a simple blood test. The anaemia itself is usually very mild, does not lead to any problems and does not require any treatment. In particular, there is no benefit in taking extra iron.

Neonatal hypotonia (85%)

At birth, the children are usually floppy and it is often apparent in the first 6-9 months that the baby's development is delayed. Drooling is very common in ATR-X, particularly in young children. The open mouth associated with facial hypotonia no doubt is an important factor, as is their reluctance to swallow even with a mouth full of saliva.

Genital abnormalities (80%)

Genital abnormalities may be very mild, such as undescended testes or deficient prepuce, but the spectrum of abnormality extends through hypospadias and micropenis to ambiguous or female external genitalia. The most severely affected children, who are clinically defined as male pseudo hermaphrodites, are usually raised as females. In such cases, dysgenetic testes or streak gonads have been found intra-abdominally. In cases with ambiguous genitalia, the assignment of gender will usually have been decided prior to the diagnosis of ATR-X being made. The possibility of undescended testes should be assessed, if required orchidopexy should be carried out. Intra-abdominal testes, which are usually dysgenetic, should be removed because of the long-term risk of malignancy.

Skeletal abnormalities (90%)

Skeletal abnormalities are rather diverse and may become apparent as the children grow. Occasionally a child may be born with a club-foot deformity. Some joints especially the fingers may be in a fixed, flexed position. Curvature of the spine can occur with age and should be checked for.

Cardiac defects (20%)

A few children are born with abnormalities of the heart. These may involve holes between the chambers of the heart, or abnormalities in the heart valves. Echocardiography should be considered at the time of diagnosis. Sometimes surgical correction may be necessary.