

## Monosomy 13q syndrome

### The disease/injury/diagnosis

Monosomy 13q syndrome is a chromosomal disorder characterised by intellectual disability and congenital malformations affecting the skeleton and major organs such as the heart, brain, and eyes. Another name for the disorder is 13q deletion syndrome.

### Incidence

Over 180 individuals with monosomy 13q syndrome have been described in the international medical literature. A few Swedish cases are known.

### Aetiology of the disease/injury

In monosomy 13q syndrome a portion of the long arm (q) on chromosome 13 is missing (deleted or monosomic). The monosomic chromosome is usually found in all cells in the body, but occasionally the deletion is only present in some cells. The result is a mixed population of cells where some are normal and some are not, a condition known as mosaicism.

The gene mutation sometimes occurs before conception, during the formation of gametes (eggs or sperm). The disorder may also result from a chromosome rearrangement known as ring chromosome 13, meaning that parts of both arms of chromosome 13 have been lost and the two broken ends have reunited to form a ring. As the genes on the short arm of chromosome 13 are relatively insignificant in comparison with those on the long arm, the clinical manifestation is similar to that seen in monosomy 13q syndrome.

Sometimes the cause of the syndrome is a balanced chromosome rearrangement in one of the parents, for example a translocation or an inversion. In a translocation, two chromosomes have exchanged genetic material. A child with monosomy 13q syndrome whose parent is a carrier of a balanced translocation will have a chromosome 13 deletion and an extra segment from another chromosome, a condition known as trisomy. More information on translocation and inversion is given below, under "Heredity".

### Heredity

The chromosome abnormality causing monosomy 13q syndrome often occurs during the formation of gametes, which means that the condition is not inherited. As each parent has two normal copies of chromosome 13, the risk that they will have another child with the disorder is minimal. Similarly, the risk in subsequent pregnancies is low in cases of ring chromosome 13, as this mutation usually occurs in the early stages of embryonic development.

When the syndrome is caused by a translocation, inversion or some other chromosome rearrangement in one of the parents, there is a risk that siblings will also be affected. A translocation takes place when segments from two different chromosomes switch places. As no

chromosomal material is lost or added in the process, the translocation is referred to as balanced. An inversion occurs when a chromosome breaks in two places and the segment between the two ruptures is twisted 180 degrees. As a consequence, the DNA sequence in the segment is reversed.

A carrier of a balanced translocation or an inversion is usually asymptomatic, but problems may occur when gametes are formed. In the formation of reproductive cells, the number of chromosomes decreases by half, from 46 to 23, as eggs or sperm cells only contain a single chromosome copy from every pair (new chromosome pairs are formed at conception). For a translocation to be balanced in the child of a healthy carrier, both the altered chromosomes need to be distributed to the same gametes. If this does not occur the child will be born with one extra chromosome segment (a trisomy), while another will be missing (monosomy).

There is a risk that a parent with a balanced translocation or a chromosome 13q inversion will have more than one child with the syndrome. If the translocation is carried by the mother, the risk is 10-15 per cent, and by the father, 2-4 per cent.

## **Symptoms**

The severity of monosomy 13q syndrome depends on the size and location of the deletion. A large deletion will result in a more severe form of the disorder.

Infants with monosomy 13q syndrome will have low birth weights owing to intrauterine growth restriction. On average, newborns with a deletion comprising half the long arm of chromosome 13 weigh 2000 g, are 40 cm long, and have a head circumference of only 30 cm. Hypotonia (low muscle tone) is common. The condition usually improves in the first few years of the child's life, although problems may persist. Poorly developed oral motor skills and sucking problems often lead to feeding difficulties. In some children, cleft palate exacerbates the feeding problems.

Although most children with monosomy 13q syndrome resemble their parents and siblings, their appearance may include certain traits associated with the disorder. The eyes are often small (microphthalmia), and wide set (hypertelorism). A thin forehead, underdeveloped midface and a high-arched palate are common. Some children have cleft palate. The mouth and nose are usually small and the nasal bridge may be flat. The ears may be low set and the lower jaw small (micrognathia). The neck is often short, and the hairline low. The teeth may erupt irregularly, and are sometimes malpositioned. Tooth enamel defects are common.

Large deletions increase the risk of severe organ damage and the life expectancy of newborns may be shortened. Birth defects may occur even if only a small part of chromosome 13 is missing, but these can usually be treated surgically.

### **The heart**

Many children with the syndrome have congenital heart defects. A common cardiac anomaly is a hole in the wall (the septum) between the right and left atria (atrium septum defect, ASD). Other common defects include a hole in the septum between the ventricles of the heart (ventricular septum defect, VSD), a narrowing of the pulmonary valve (pulmonary stenosis) or of the aorta (coarctation of the aorta), open ductus (patent ductus arteriosus, PDA), or Tetralogy of Fallot, which is a combination of four heart defects.

### **The brain**

Almost all children with the syndrome are developmentally delayed. Many have moderate to severe intellectual disabilities, while others are only mildly affected. In rare cases, the deletion is small enough not to affect cognitive development. Some children have autistic traits or behavioural disorders. Although these children resemble each other in outward appearance, their development is highly individual. Some of them learn to talk, while others use alternative means of communication.

Some children have epilepsy, and various brain anomalies may interfere with normal development. Premature closing of the cranial sutures (craniosynostosis) may result in an

abnormal head shape, and a few children have hydrocephalus. Some are spastic and may be affected by leg and foot paralysis (spastic diplegia). Other examples of brain abnormalities include underdeveloped brain (cerebral hypotrophy), underdeveloped or absent corpus callosum (the band of nerve fibres connecting the two sides of the brain), underdevelopment of the cerebellum (cerebellar hypoplasia), or mater dura or brain tissue hernias (encephalocele).

Children with a large deletion comprising half the long arm of chromosome 13 often have holoprosencephaly, meaning incomplete cleavage of the brain into cerebral and lateral hemispheres. The presence of holoprosencephaly usually indicates loss of chromosome segment 13q32, which is the location of a gene known as *ZIC2*. This gene is believed to play a vital role in brain development.

A few children with the syndrome also have spina bifida (myelomeningocele).

### **The skeleton**

Some children are born with luxation (dislocation) of the hip joint, clubfoot or vertebral abnormalities. Thumbs may be absent, underdeveloped or abnormally positioned. The little finger is often short and bent inwards (clinodactyly). Foot and toe defects such as webbed toes (syndactyly) may be present. Hand and foot abnormalities are associated with the loss of chromosome segment 13q32.

### **Other birth defects**

The kidneys may be absent (renal agenesis), malformed (hydronephrosis), or abnormally positioned (ectopic kidneys). Genitalia may be underdeveloped, and the testes sometimes fail to descend into the scrotum in affected males (retention testis). The thymus gland, the thyroid, the pancreas and the adrenal glands may be underdeveloped or absent.

The anus may be malpositioned or absent (imperforate anus). Children with the syndrome occasionally have Hirschsprung's disease, characterised by poor intestinal function owing to absent nerve cells. The gall bladder may be missing, and the small intestine is sometimes abnormally narrowed. Some children have gastric reflux, a backflow of acid from the stomach into the oesophagus. Vomiting is a common symptom, and the children may fail to thrive. Asthma-like symptoms may present if stomach acid flows into the trachea.

### **The eyes**

About one third of children with monosomy 13q syndrome have iris and choroid coloboma, meaning that parts of these eye structures are absent. Strabismus (squinting) is common and many children have nystagmus (involuntary oscillating eye movements). Glaucoma, cataracts and cloudy lenses are other vision problems associated with the syndrome. In rare cases, eye problems are severe enough to result in blindness.

A 13q14 deletion increases the risk of developing a malignant tumour in the retina of the eye, a condition known as retinoblastoma. Children with the mosaic variant of the syndrome are also at risk, although not everyone with the deletion develops the malignancy. Retinoblastoma is generally discovered before the child has reached the age of four years, and in most cases the condition is diagnosed early, between the ages of four and six months. The condition normally affects both eyes, but in monosomy 13q syndrome only one eye is affected. The prevalence is higher in boys than in girls (2:3).

### **Other symptoms**

Two genes regulating blood coagulation (*factor VII* and *factor X*) are located on the tip of the long arm of chromosome 13. In children with a translocation involving this area, the concentration of these coagulation factors may be low. However, there is no indication that the condition increases the risk of bleeding or causes any other problems.

Some individuals with monosomy 13q syndrome are deaf. Adults with the syndrome have short stature and sometimes a small head (microcephaly). The oldest person with the syndrome to be described in the medical literature had reached the age of 67.

## **Diagnosis**

The diagnosis is confirmed by performing a chromosome analysis of cultured blood cells. The deletion size and location should be established, for example in order to judge the risk of retinoblastoma (more information about this condition is found under "Symptoms").

A chromosome analysis of both parents should be carried out in order to detect if they are carriers of translocations or inversions. If either parent is identified as a carrier, his or her relatives will be offered testing, as they too may be carriers of the translocation or inversion.

Prenatal diagnosis is possible.

## **Treatment/interventions**

There is currently no cure for monosomy 13q syndrome, but there are various ways of relieving the symptoms.

If the child fails to thrive owing to feeding difficulties, a nutritionist or speech therapist may provide valuable support and assistance in establishing feeding routines. The child's growth should be carefully monitored. Growth hormone deficiency is rare, but in cases of extremely short stature hormone production evaluation is recommended.

Early contact with a plastic surgeon is required if the child has cleft palate or a combination of cleft lip, jaw and palate. Cleft deformities are treated over a number of years as several surgical interventions are required. The results are usually excellent.

A paediatric dentist should monitor tooth eruption and assess the need for orthodontic treatment. Tooth enamel defects are treated by covering the teeth with a protective coating.

### **The heart**

As congenital heart defects are relatively common, all children with the syndrome should be examined by a paediatric cardiologist. Ultrasonography is used to detect any cardiac anomalies. Some heart defects (such as ASD and VSD) improve on their own, while others require surgical intervention. Children with heart anomalies need to be carefully monitored.

### **The brain**

Epilepsy is a condition of recurring cramps caused by sudden surges of electrical activity in the brain. Seizures may take many forms and the diagnosis should specify the type. This is done in an EEG, a brain wave test. The activity of the brain is monitored over a short or extended period of time, either in a neurophysiological laboratory, or over a number of days in a regional paediatric clinic. An MRI scan (magnetic resonance imaging) may also be used to confirm the diagnosis. Normally, epilepsy can be treated medically. Evaluation and treatment is carried out by a paediatric neurologist or a habilitation specialist.

Some children have craniosynostosis, meaning premature closing of the cranial sutures (skull bones). This skull defect inhibits the growth of the brain. Abnormal increase of head circumference is a sign of hydrocephalus. The condition is treated by inserting a shunt, a flexible tube used to divert accumulated cerebrospinal fluid from the brain to the abdominal cavity.

As brain anomalies are common, it is recommended that all children with the syndrome undergo an MR scan between the ages of one and two. Most brain abnormalities cannot be treated, but accurate diagnosis may help explain delayed intellectual development and seizures. Surgery is rarely considered, but may be an option if a minor malformation causes severe seizures that do not respond to treatment. Spina bifida requires early surgery to close the hernia and follow ups should be scheduled. Spina bifida is associated with an elevated risk of developing hydrocephalus.

### **The skeleton**

Hip luxation is usually discovered early. The condition is treated with splints, but surgical intervention is sometimes necessary. Clubfoot is evident at birth and is usually successfully treated with splints or a plaster cast, although surgery may be required. Vertebrae abnormalities seldom cause any major problems, but each case must be evaluated individually. Underdeveloped kneecaps rarely pose a problem, but in cases of knee luxation (dislocation), surgical intervention may be necessary. Finger abnormalities are usually minor and of no practical consequence. However, if the thumb is absent or if its position impairs the grip, a hand surgeon should be contacted. Sometimes hand bones or toes have fused, but as these anomalies rarely interfere with hand or foot function, surgery may be considered unnecessary.

### **Other malformations**

Kidney abnormalities and hydronephrosis (backflow of urine into the uterus) should be carefully investigated, and surgery, performed by a paediatric surgeon or urologist, may be necessary. Surgery is also used to treat testes that have failed to descend into the scrotum.

Gastrointestinal malformations are investigated by a paediatric surgeon. In cases of Hirschsprung's disease, the abnormal part of the colon is removed. The procedure can usually be carried out immediately, but in some cases a temporary colostomy is performed. Umbilical and loin hernias are also treated surgically. In cases of suspected gastric reflux, the oesophagus pH level is monitored for 24 hrs. The condition usually responds well to medical treatment, but surgical intervention is sometimes required.

### **The eyes**

Eye abnormalities are common, and owing to the risk of retinoblastoma the child should be examined by an ophthalmologist at an early age. Iris coloboma is common, but vision is usually only impaired if the innermost parts of the eye or the optic nerve are affected. Strabismus can be treated with a patch over the normal eye in order to train the squinting eye. Surgery is sometimes required.

Nystagmus does not require treatment. Glaucoma patients should be monitored closely and the condition is usually treated with eye drops. Cataracts and opaque lenses require surgical intervention. In cases of severe vision impairment or blindness, a vision consultant and a low vision resource centre should be contacted. If the child has retinoblastoma, the eye is usually replaced by a prosthetic eye. Radiotherapy and chemotherapy are treatment options, and nowadays most children with retinoblastoma are cured.

### **Other interventions**

Assessment by a paediatric endocrinologist is required if hormone-producing organs such as the adrenal glands or the thyroid are underdeveloped or absent. Hormone supplements are sometimes given.

Bleeding problems should be investigated as the child may be deficient in coagulation factors VII and X. A coagulation investigation should also be carried out before surgery.

All children with the syndrome should be examined by an ear specialist or an audiologist.

### **Treatment and training, etc.**

Early contact should be established with a paediatric treatment and training centre, bringing together various professionals with experience in working with disabilities. The habilitation physician at the centre is responsible for medical care. An occupational therapist evaluates the child's level of functional disability and assesses the need for aids, equipment and new routines to make daily life easier. A physiotherapist evaluates motor function and can put together a training programme for optimising movement. A guidance counsellor provides support to the family and gives information about national and regional provisions and resources. A speech therapist evaluates and trains language and communication skills, and provides advice on how to cope with swallowing difficulties. A psychologist evaluates and supports the child's development and is available for counselling to parents and siblings.

Children with intellectual disability should have early access to special education. The child's individual capacities and limitations should guide the choice of daycare, school and after-school

facilities. During the preschool years, a special education teacher and the staff at a play therapy centre will provide access to special toys and other educational resources adapted to the individual needs and interests of the child. As the degree of intellectual disability varies from case to case, it is not possible to give any general advice on which supportive measures should be taken, or how to select a suitable school.

Special education should include speech and communication training. Some children learn to speak, while others communicate using sign language or other forms of alternative communication. An occupational therapist, a speech therapist and a special education teacher all participate in assessing the need for alternative communication strategies and trying out communication aids.

On learning that a child has a rare chromosomal disorder, many parents undergo an emotional crisis. In this situation, the ability to deal with information about the syndrome and available support is limited. It is therefore vital that the information is repeated on later occasions and that the parents are given time to ask questions and ventilate their concerns. All parents should be offered support from a counsellor or a psychologist in the paediatric rehabilitation services. Parents should also be offered contact with other families in the same situation who are willing to share their experiences.

Many families use respite care services to be temporarily relieved of tasks associated with caregiving, and to find an opportunity for rest and recreation. The child may then remain in the home with a personal assistant, or stay with a support family or at a short-term respite care facility. The family may need assistance in coordinating various interventions and activities.

Adults with the syndrome need continued treatment and support to manage their daily lives.