Sotos Syndrome

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Background

Sotos syndrome is an uncommon condition that affects approximately one in fourteen thousand of the population. Until recently, doctors would diagnose Sotos syndrome on the basis of several common features that include characteristic facial appearance, a degree of learning disability, increased head circumference and large stature. A sample of blood was often taken for genetic testing that could rule out similar syndromes and an x-ray of the wrist could be used to check for advanced bone growth which is another characteristic of Sotos syndrome. However, in 2004 a Japanese research team discovered that most children with Sotos syndrome have a fault in the NSD1 gene and a genetic test is now available that can be used to give a definitive diagnosis. Unfortunately, approximately ten percent of the children who had been diagnosed with Sotos syndrome before the genetic test was available appear to have no abnormality in the NSD1 gene. This may be because they have a fault in the gene that cannot be detected by the test or because they have a fault in another gene that is related to NDS1.

There are several other syndromes which cause increased stature and may be confused with Sotos. They include Weaver, Bannayan-Riley-Ruvalcaba, Beckwith-Wiedemann and Simpson-Golabi-Behmel syndromes. However, the genetic testing can now be used to distinguish between these various conditions and in most cases there is no doubt about the diagnosis. As many paediatricians have little or no experience of Sotos syndrome it is often the case that children do not receive a diagnosis for many years and it can be an enormous relief to finally have an explanation for a child's problems.

From a parent's point of view there is very little about the way the syndrome affects the child that is of any serious concern. There is no reason to suppose that the child will suddenly deteriorate in health or ability and it is likely that they will have a normal lifespan. Common problems associated with Sotos in early childhood include constipation, tooth decay and ear, nose and throat infections. However, a few children do experience more serious conditions such as Scoliosis (curvature of the spine), epilepsy and congenital problems with the heart or kidneys which all require specialist treatment.

All children with Sotos syndrome have some degree of learning difficulty but this may range from very mild to very severe. In many cases, a child that has been very slow to reach the major milestones such as walking and talking will continue to develop (at their own pace) and eventually catch up with their peers. Indeed, it has often been said that having Sotos is like "being on a slower train".

Some of the children affected by the syndrome go almost undetected in the ordinary population and a few parents of the more able children choose not to inform schools and friends of the diagnosis in order to prevent the child being "labelled". However, other parents find that it is useful to make the condition known as it can be the key

that activates the provision of support services such as physiotherapy, speech therapy and disability living allowance.

The purpose of this guide is to describe in layman's terms what is known about the syndrome and to give some practical advice for parents of Sotos children. Although it deals with medical issues, any specific medical concerns should be referred to your GP or consultant.

History

The syndrome was first described in 1964 in an article published by Juan F Sotos and colleagues in the New England Journal of Medicine. They reported a study of five children who all had a unique group of clinical features that are now associated with the syndrome. In the early years, the condition was often referred to as Cerebral Gigantism but this term has largely been superseded by Sotos syndrome. Several other studies were carried out, including those by Dr Trevor Cole and colleagues in the UK, which helped to clarify additional features which were often associated with the syndrome. It was originally thought that there might be an increased risk of children with Sotos syndrome developing certain childhood cancers as both are associated with rapid growth. Although links have been confirmed with other overgrowth syndromes (eg liver and kidney tumours with Beckwith-Wiedemann and breast cancer with Bannayan-Riley-Ruvalcaba syndromes) there is now sufficient evidence to suggest that children with Sotos syndrome do not have a significantly greater risk of developing cancer than the general population.

Children were originally diagnosed purely on the basis of their clinical features and it was not until 2002 that a team of Japanese geneticists discovered that defects in the NSD1 gene were responsible for the syndrome. A routine genetic test has now been developed that can be used to confirm a clinical diagnosis of the syndrome. Research is also continuing in an effort to find a genetic explanation for those children who have a clinical diagnosis of Sotos syndrome but no apparent defect in the NSD1 gene.

Diagnosis and Cause

The age at which the parents of Sotos syndrome first seek medical advice varies significantly. Occasionally, a baby is diagnosed at birth if a paediatrician has had previous experience of Sotos syndrome and recognises the distinctive facial features which can be as characteristic as those associated with Downs Syndrome. More often, it is not until the child starts to miss major developmental milestones that the parents or health professionals instigate clinical investigations. These may be quite protracted and it is not unusual for children to eventually be given a diagnosis after several years of investigations. Indeed, it is not known how many children with Sotos syndrome are never diagnosed.

An initial diagnosis will usually be made by a consultant paediatrician or geneticist whose judgement is based on a number of characteristics of the syndrome that are identified in the patient. The doctor will take a full case history and the characteristics that are usually considered relevant include: accelerated growth, large head circumference, advanced bone age, facial features, large hands and feet, poor co-

ordination and developmental delay. These are known by doctors as the diagnostic criteria.

A number of other syndromes share some of these diagnostic criteria, as they are common variables in the population at large. Therefore to make a firm diagnosis most, if not all of these features should be present. There are even a few syndromes where all the above features appear to be present and subtle differences may make your doctor consider another diagnosis. It is important to remember that some of your child's symptoms may have nothing to do with Sotos syndrome.

Most clinical diagnoses of Sotos can now be confirmed with the genetic test but in approximately ten percent of children, the test results prove to be negative. In these circumstances the doctor will probably describe the child as being Sotos-like.

The causes of the NSD1 genetic defects are not known and there is no evidence to suggest that the condition resulted from something that the mother did or not do, eat or not eat, during pregnancy. Many Sotos babies have a difficult birth but this results from their large size and increased head circumference and is definitely not the cause of the syndrome.

Physical Characteristics

Head and Face

The forehead is often broad, with the hairline starting further back than average and the nose bridge between the eyes being flatter than normal. The spacing between the eyes can be relatively wide and there is often a downward slant at the outer edges of the eyes. The chin tends to be pointed or jutting and sometimes there is a slight difference in length between the jaws, so that when the mouth is closed the upper set of teeth does not exactly meet the bottom set.

The head is invariably larger than average which can lead to the suspicion of hydrocephalus (water on the brain) although this is rarely present. The shape of the head varies but there is often a high, broad forehead which has been described as resembling an inverted pear. The large head size becomes much less apparent as the child grows, although a continual problem may be experienced by parents trying to squeeze heads through tightly fitting clothing.

Growth and Puberty

Sotos babies tend to be significantly larger than average due to excessively rapid prenatal growth. During the first few years of life the children continue to grow rapidly and may well remain above the 97th centile on growth charts for many years. The bone age may also be advanced although this varies from child to child. The bone age gives an indication of the maturity of the skeleton and is assessed from an x-ray of the wrist. Advanced bone age is a normal variation that can be seen in the general population and does not necessarily indicate a problem with the bone. Tooth development may also be advanced and the first milk teeth will often appear at the age of three months.

As the child approaches puberty the rate of growth slows and will have stopped completely by the end of puberty. Girls tend to grow approximately two inches after the start of their periods and although boys will continue to grow later into their teenage years they also stop growing as the male hormone levels increase. The onset of puberty is partially related to the bone age and it appears that most children with Sotos syndrome reach puberty at the low (early) end of the normal range. Consequently, Sotos children tend to stop growing before their peers and are therefore not excessively tall as adults. However, most of them will be slightly taller than would be predicted from the height of their parents.

Routine measurements of height and weight are taken in most paediatric clinics which allow careful monitoring of growth and a single measurement of bone age may prove useful. It is possible to influence the final height of a Sotos child by prescribing hormones to induce an early puberty. However, any potential benefits must be balanced against the emotional immaturity of the child and in most cases, intervention of this type would not be recommended.

Arms, Hands and Feet

Sotos children tend to have relatively long limbs with large hands and feet. The extra length of the arms can be judged by standing the child against the wall with arms outstretched and measuring the span from fingertips to fingertips. Although most children have a span that is similar to their height, those with Sotos syndrome will typically find that their span is significantly greater than their height. These long arms can cause practical problems for parents when buying clothes, particularly items such as school blouses or shirts.

The hands and feet are also large and can sometimes have an extra layer of fat that makes them seem fat and podgy. The purchase of suitable shoes can be a problem especially as most Sotos children have poor manual dexterity and struggle to tie laces. The common experience of flat feet and a tendency to roll in and out at the ankles can lead to rapid wear of the shoes. In recent years, the availability of large, fashionable shoes with Velcro fastenings has improved.

Co-ordination, Tone and Posture

Sotos children are described in the medical literature as being clumsy and poorly co-ordinated with low muscle tone. The lack of co-ordination steadily improves with time but parents should expect their children to struggle with any activity that requires well developed gross or fine motor skills.

Walking can be delayed significantly with the typical Sotos child taking their first steps between the ages of eighteen and twenty seven months. Initially balance will seem poor with the child falling when turning suddenly or tripping over uneven surfaces. This is not surprising as they will be so much larger than the average child when starting to walk. A few children retain a dislike of walking long distances although there is no obvious medical reason for this. There is no evidence that exercise would cause harm and it should therefore be encouraged.

Lack of co-ordination and hypotonia (floppy muscles) of facial and jaw muscles can lead to drooling and a dislike of eating any foods that need chewing. The drooling will cease as the muscle tone improves but the inability to suck sweets and the tendency to swallow them whole may persist for some years. Parents trying to transfer a baby onto solid food may well find that the stage of pureeing foods will be longer than they might expect. Some babies may have a poor suck or other early feeding problems.

Toilet training can be very delayed and it is not unusual for Sotos children to still be wearing nappies when they start school. Bed wetting can persist into late childhood and is probably a result of the natural relaxation of the muscles when in deep sleep. If this is a problem, your health visitor may be able to help with large size nappies, pads and plastic covers for the bed. Constipation is a common problem throughout childhood and may again be related to the low muscle tone associated with Sotos syndrome.

The posture of Sotos can be rather poor in the early years with a slight stoop, the head jutting forward slightly and the knees bent. This can also be attributed to low muscle tone and improves with regular physiotherapy and the natural development of the child. Swimming, dancing and other exercises are useful as well as enjoyable.

Co-ordination problems may continue throughout life and activities such as cycling, skating and ball sports can be very challenging for those with Sotos syndrome. However, most of the children are very strong despite their lack of co-ordination. One adult affected by the syndrome commented that they would choose not to learn to drive because they felt that they lacked the co-ordination required to react to emergencies. The same adult had successfully learnt to type.

Other Features

There are several other features that seem to be common in children with Sotos which can be summarised as follows

- Divergent squint (usually disappears without treatment)
- Very high pain threshold (children may not seem to notice fractures of bones)
- Flat finger and toenails
- High arched palate (roof of mouth)
- Poor control of temperature (may be unusually hot or cold)
- Excessive thirst or hunger
- Sensitivity of scalp

<u>Potential Health Problems</u>

The health of Sotos children is usually very good, especially after the first five years and there is no evidence that they will be any more likely than the general population to suffer from poor health as adults. However, there are a few health problems that appear to be associated with the syndrome and about which parents should be aware.

Neonatal problems

A high proportion of babies born with Sotos syndrome suffer from jaundice, hypotonia (floppiness) and feeding difficulties. However, these problems usually resolve spontaneously and no medical intervention is required.

Infections

Although most children suffer from urinary and respiratory tract infections, these appear to be more prevalent in children with Sotos syndrome. For example, a tendency to have narrow external ear canals and abnormal internal ear canals (Eustachian tubes) can increase the chance of ear infections. It is not unusual for Sotos children to have persistent ear infections that require treatment with antibiotics and the fitting of grommets. Urinary tract infections are also common and are occasionally related to congenital deformities such as the absence of a kidney, narrowing of the urethra or flow of urine from the bladder back to the kidney.

Although these infections can be treated effectively with antibiotics they can potentially result in permanent damage if left untreated. Many Sotos children have a very high pain threshold and infections can become quite serious before it is obvious that the child is unwell. This situation is exacerbated by the delayed speech and parents should always seek medical attention if their child has an unexplained high temperature.

Epilepsy

It is not uncommon for Sotos children to suffer from epilepsy at some stage during their childhood. With younger children (typically under the age of five), febrile convulsions can occur when the child has a high fever. This type of epilepsy affects approximately one in twenty of the general population and is caused by immaturity of the temperature-lowering mechanism in the brain. The child should be kept cool and paracetamol should be used to reduce fever in children known to be susceptible to febrile convulsions.

Some Sotos children are affected by Grand Mal seizures which are not related to body temperature and can potentially occur at any time. In most cases it is not known what triggers these fits although occasionally they can be linked to diet or external effects such as flashing lights. The fits can be very frightening for parents and the child may become rigid or have uncontrolled twitches and jerks. Breathing usually becomes very shallow and may even stop completely for a short time. After the fit, the child will typically lose control of their bladder and bowels and be very drowsy for many hours. There are a range of drugs that can be prescribed to reduce the frequency of seizures although in most cases, the child will grow out of the condition after a few years.

Scoliosis

This is a condition in which the spine is bent to one side and affects approximately thirty percent of Sotos children. It typically starts to develop in children of primary school age and parents should ask their GP or paediatrician to check the spine regularly. In many cases no treatment is required but if the curvature becomes too

severe it may be necessary for the child to wear a brace or even have surgical correction. If left untreated, the curvature can worsen and damage to the heart, lungs and pelvis can occur.

Congenital problems

A few Sotos children have congenital (present at birth) abnormalities of the brain, heart and kidney. The differences in the structure of the brain are detected using MRI scans and are typically quite subtle. Heart and kidney abnormalities may also be relatively minor but in a few cases surgical intervention is required.

Genetics

Sotos Syndrome is an autosomal dominant condition which means that if either one of the parents has Sotos, there is a fifty percent chance that each of their children will inherit the condition. In the unlikely event that both parents had Sotos, the risk of their children inheriting the condition would be greater than fifty percent. If the child of an individual with Sotos does not have the syndrome, there is no possibility of the condition missing a generation and being inherited by grandchildren.

There is absolutely no reason why adults with Sotos should not have children and indeed there are several families in the UK with Sotos syndrome in more than one generation. Genetic counselling could be offered to those wishing to start a family as with any other inheritable condition.

The abnormality on the NSD1 gene that causes Sotos happens very soon after fertilisation of the egg and is essentially a mistake in the copying of the genetic information from one of the parents. Therefore, the chance of a couple having another child with Sotos syndrome is the same as for any other couple (approximately one in fourteen thousand) provided they do not have the syndrome themselves.

Development

There is invariably some degree of learning disability associated with the syndrome but this is very variable and an estimate of the possible range of IQ is 20 – 120. Typically the average child affected by Sotos syndrome will have an IQ at the low end of the normal range and can be considered to have a moderate learning disability. A general prediction of a child's final level of attainment can not be given as it will be directly related to the basic IQ and the amount of extra support, stimuli and quality of education given over the formative years. Some adults with Sotos syndrome lead self-supporting independent lives but others require residential care throughout their life.

Early development is frequently delayed with many of the children first coming to the attention of medical specialists as a result of failing to meet developmental milestones such as crawling and walking, although these will be strongly influenced by a child's low muscle tone, size and co-ordination. Language development may also be delayed significantly and expressive language skills seem to be particularly affected. The vast majority of Sotos children do eventually develop normal verbal communication but many benefit from regular speech therapy. Some children attend schools that

specialise in teaching those with language difficulties and others use the sign language Makaton to compliment verbal communication in the early years.

Concentration is often poor with the young Sotos child unable to settle to any one task for more than a few moments. This can lead to problems in early schooling as the children tend to be much larger than their peers and therefore disrupt the class as they leave their seats. Concentration inevitably improves with maturity. Visual stimuli are good for the children and many will look at books or television for hours, despite otherwise poor concentration ability. The children do seem to be particularly adept at using video recorders, computers and other electronic equipment.

Reading tends not to be too much of a problem but handwriting can be very large and immature due to the very poor fine motor skills mentioned earlier. Mathematics invariably causes considerable difficulties for Sotos children as they are unable to understand abstract concepts and have problems with spatial awareness, sequencing and proportionality. Time can be a source of confusion and many Sotos children refer to any time in the past as being “yesterday” and all future events as being “tomorrow”.

Most of the developmental issues mentioned in this section can be attributed to physical or social immaturity and skills are simply acquired at a slower pace than most of their peers. Although most Sotos children will benefit from speech and occupational therapy, they will inevitably continue to develop and reach milestones in their own time.

Social and Behavioural Issues

Sotos children are affectionate and loving and work very well on a one-to-one basis with adults. Teaching them and working with them is a very rewarding experience. However, they are often not very comfortable with children of their own age and tend to seek the company of adults or children from a very different age group. This may be for a variety of reasons such as poor expressive language, size, social immaturity and lack of self-confidence. Many parents have said that their child would prefer to play with or look after the younger ones.

Some parents have said that their children seem to lack any close friends of their own age and this seem to be a problem that persists into adolescence and possibly adulthood. Finding ways to include children with Sotos syndrome may be challenging but is very rewarding when successful.

A continual problem for teachers, parents and the general public is that normal expectations for standards of behaviour and achievement are instinctively based on size and apparent physical maturity. A child who is struggling to achieve an age-appropriate level of behaviour and attainment may feel demoralised when an adult overestimates their age and has unreasonable expectations. Parents can find it a trial in shops and other public places where the same behaviour that would be acceptable for a three year old (such as running down the aisles of the shop) is not acceptable when their child happens to be the size of a seven year old. Acceptable norms of behaviour do need to be enforced by parents from an early age. The boys, in particular, can be

very strong and it may well be impossible for the mother to physically restrain the child from the age of seven or eight.

As with all children, the behaviour can vary from year to year. The developmental stage commonly known as the “terrible twos” can be experienced when the child is three or four and the resulting tantrums can appear to be much more serious because of the extra size of the child. Sotos children do tend to be easily frustrated and this can manifest itself in aggressive behaviour towards their peers. This frustration can probably be attributed to poor verbal communication skills in most cases and it can be expected that the temper tantrums will disappear as the child matures. Indeed, for most families the early childhood tantrums are just a passing phase and the usual mixture of persuasion and encouragement teaches acceptable norms of behaviour. However, in a few families the behavioural problems persist and are the most troublesome aspect of the syndrome. In these circumstances professional help may be required.

The poor concentration that is common amongst the younger children can be combined with a general restlessness and perhaps a tendency to roam without fear. This does require extra vigilance on the part of the parents to ensure that the child is occupied safely. Some Sotos children have been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and a few have been prescribed methylphenidate (Ritalin, Concerta) to help with this aspect of their behaviour.

Most children with Sotos syndrome show many of the behavioural characteristics that are normally associated with autism. These include repetitive patterns of play, over-reliance on routine, anxiety, sensory overload, poor social interaction and lack of imagination. However, recent studies have shown that they do not normally exhibit enough of the criteria for a formal diagnosis of autism to be considered. The autistic-like behaviour persists into adulthood and further research is required to define more precisely the behavioural characteristics that are associated with Sotos syndrome.

Summary

The preceeding pages have dealt with all the features and health problems that are associated with Sotos syndrome and it is hoped that parents will be reassured that there is nothing frightening waiting to surprise them. No one child will have all the characteristics mentioned and indeed many appear to have very few. Other families will have already experienced almost anything that you are likely to encounter and most are willing to share their experiences with others.

Many families have stated that the parenting of a child with Sotos syndrome becomes very much easier as the years go by and the child is able to be more independent. Health also seems to improve significantly after the first few years. The early concerns about a link between Sotos syndrome and childhood cancers have never materialised and the most serious health problems that may be encountered are probably epilepsy and scoliosis, both of which can be easily treated.

Further Reading

1. http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=117550

A comprehensive article produced by the "Online Mendelian Inheritance in Man" project that is run by the American National Institute of Health. This web page is regularly reviewed and updated and currently contains references to fifty three academic papers.

2. http://www.gghjournal.com/volume22/3/featureArticle.cfm

A very recent paper published by an American team that focuses on the genetics of Sotos syndrome.

3. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=sotos

This recent paper by Professor Nazneen Rahman, Dr Trevor Cole and Dr Kate Tatton-Brown gives a detailed description of Sotos, an explanation of the genetic research and useful guidelines for management of the syndrome.

4. http://www.nature.com/ejhg/journal/v15/n3/full/5201686a.html

Another recent paper by Professor Rahman and Dr Tatton-Brown which contains a comprehensive section on the molecular and genetic basis of Sotos syndrome.

5. http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=64324

This paper gives a full description of the NSD1 gene but would require detailed knowledge of genetics to be of much interest.

6. http://www.well.com/user/sssa/index.html

The home page of the Sotos Syndrome Support Association which is the US equivalent of the Child Growth Foundation.

7. http://en.wikipedia.org/wiki/Sotos_syndrome

A short and simple account of Sotos syndrome in the Wikipedia encyclopaedia

These articles all include references to many other papers, most of which contain very detailed genetic information. In many cases it is only possible to view abstracts and the full papers are only accessible with an online subscription to the relevant journal.