

Sotos syndrome – Case report of a rare genetic disorder

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ABSTRACT

Sotos syndrome is a congenital disorder that is characterised by pre and post natal overgrowth, mental retardation of variable degree, advanced bone age, and distinctive craniofacial features like macrocephaly frontal bossing and high hair line. Recently several reports have presented that haploinsufficiency of the gene for NSD1 (the nuclear-receptor-binding SET-domain-containing protein 1) at 5q35 causes Sotos syndrome. This syndrome is often difficult to diagnose due to the substantial similarities with the other ill defined overgrowth phenotypes. Here we report a rare case of Sotos syndrome describing the clinical features and the craniofacial findings usually manifested in these patients.

KEY WORDS: Sotos; Mutation; Syndrome; Overgrowth

INTRODUCTION

Sotos syndrome is a juvenile overgrowth disorder. Most of the cases of this syndrome have been sporadic. Although the first patient described to be having the features of Sotos syndrome may have been reported in the year 1931, this syndrome was first described by Sotos et al in 1964 [1,2]. It has been reported worldwide across all ethnic groups. Cole and Hughes in 1994 established four major diagnostic criteria [1,3] based on systematic assessment of forty one classic cases. The major criteria's included macrocephaly, learning difficulties, characteristic facial appearance and overgrowth with advanced bone age. These clinical criteria's became the keystone for the diagnosis of Sotos syndrome up until 2002. Lately mutations and deletions of *NSD1* (the nuclear-receptor-binding SET-domain-containing protein 1) have been recognized in these cases [1,4]. This has lead to the reassessment of the features of this condition. Nevertheless, upto thirty five percent of the reported series of Sotos patients have not shown any *NSD1* abnormalities. In such cases, the possible participation of the *NSD2* and *NSD3* genes has already been excluded by sequencing [1,5].

Previously, Sotos Syndrome was well-known as “cerebral gigantism” [6,7]. Even though its variable expressivity has been clearly noticed among several cases, the classic phenotype of this syndrome is considered to be one among the most common overgrowth conditions. Perhaps, after the Beckwith – Wiedemann Syndrome, Sotos syndrome can be considered as the most common overgrowth condition. Craniofacial abnormalities in this syndrome include forehead that is broad, hairline which has been placed very high, macrocephaly, downslanting palpebral fissures, mild micrognathia and pointed chin. Renal abnormalities, cardiac anomalies, seizures, scoliosis are found in these patients with variable degrees of severity [8,9]. Variable levels of intellectual developments as well as psychomotor developments are seen. Mental retardation can sometimes be absent or may even be severe. Delay in the developmental milestones are categorised by variable degree of learning disability, clumsiness, features of autism, adaptive problems, hyperactivity disorders and attention deficit. Neuroimaging aberrations in most cases are nonspecific. Commonly reported features are hypoplasia of the corpus callosum and ventricular dilatation [10]. This syndrome carries great risk of benign or malignant tumours.

Haematological malignancies are the very common. [8]. This paper documents a 4 year-old male child diagnosed with Sotos syndrome and describes the chief clinical features, the disease-specific craniofacial, oral and dental findings, and the required dental care management for this patient.

CASE REPORT

A four year old male child reported to the Department of Oral Medicine and Radiology, accompanied by his parents, with the chief complaint of multiple decayed teeth since one year. History, as told by his uncle, revealed that the child had swelling and pain on the right side of the face few months back and progressive fracturing of the teeth since several months. The patient was previously taken to the dental hospital where the child was diagnosed with right buccal space infection and grossly decayed teeth were extracted under general anaesthesia. Post extraction period was uneventful. Medical history when elicited revealed that the child was a known case of Sotos syndrome born to a non consanguineously married couple, at term, with a birth weight of 2.2 kg. The child was born after four years of infertility treatment, with uneventful antenatal period and normal birth history. Post natal period was suggestive of jaundice on the fourth day. Phototherapy was given for three days. Right inguinal herniotomy was done at one month of age and left orchidopexy was done at one year of age. The child had seizures at the age of one year for which the child was treated with valparin, which was discontinued after four months as the child developed discolouration and chipping of teeth. Family history revealed that the child was the only child of the parents and none of the family members were affected by this disease. Parents revealed that milestones like walking, speech were delayed. Patient had poor concentration abilities and mentally the milestones appeared to be delayed. The parents also reported that they experienced feeding difficulties, constant episodes of fever, and that the child gets agitated very fast.

General and extraoral examination revealed the patient had macrodolichocephaly (Fig 1), frontal bossing (Fig 2), typical dysmorphic facies, elongated face, receding hairline, sparse eye brows, low set large ears, apparent ocular hypertelorism with downslanting palpebral fissures, sunken eyes, bilateral divergent squint, depressed nasal bridge, prominent jaw, malar flushing, mild micrognathia (Fig 1, Fig 2 and Fig 3), generalised hypotonia, blind sinus in the sacral region with no other cranial nerve deficits. Intraoral examination revealed high arched palate, multiple missing teeth, and grossly decayed and fractured teeth. The child had deposits and high caries activity indicative of poor oral hygiene. The child was non co-operative for radiographs and intraoral photographs.

Radiographic Examination: Extra oral radiographs were attempted which reveals prominent forehead (Fig 4) and significant number of his teeth were absent and very few tooth buds were visible (Fig 5) indicating that they have

either been extracted or being congenitally missing. MRI revealed cortical displacement. The indentations are more than what is usually present in a child of age 3-4 years (Fig 6). There was also decreased periventricular white matter (Fig 7). Corpus callosum is apparently of normal size (Fig 8).



Fig 1. Clinical photograph showing macrodolichocephaly



Fig 2. Clinical photograph showing frontal bossing

The patient was referred to the paediatrician and craniofacial surgeon for consultation. The clinical features and extraoral findings were confirmed. Oral hygiene instructions and counselling on dietary habits were given to the parents. The child was then referred to the Department of Pedodontics for the needful. The restorative/rehabilitative treatment are being carried out at subsequent appointments.



Fig 3. Clinical photograph showing typical dysmorphic facies, elongated face, receding hairline, sparse eye brows, low set large ears, apparent ocular hypertelorism with downslanting palpebral fissures, sunken eyes, bilateral divergent squint, depressed nasal bridge, prominent jaw, malar flushing, mild micrognathia

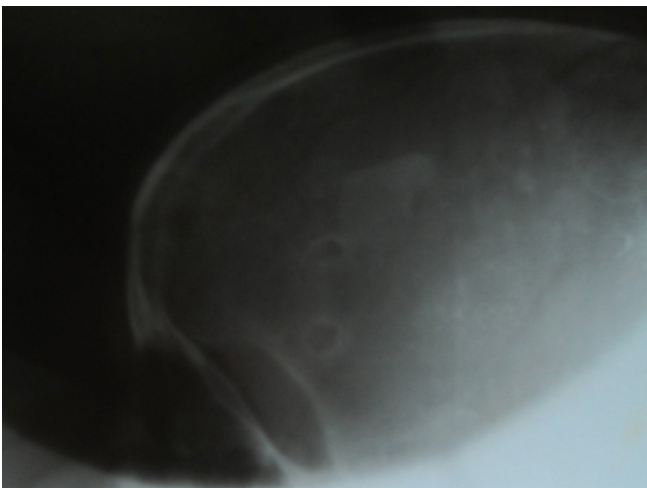


Fig 4. Extraoral radiograph showing prominent forehead

DISCUSSION

Since forty years, the diagnosis of Sotos syndrome has been largely based upon assessment of clinical features subjectively. Craniofacial features of this syndrome are distinctive, however, the other components are nonspecific. The centre point of discussion in these cases were always the lack of specific clinical features [2,11,12]. Generally in Sotos syndrome pregnancy is recorded as normal. In several cases pre-eclampsia or toxemia may be reported [2,12]. The infants are large for their gestational age although their mean gestational age is normal which is approximately 39 weeks. According to Cole and Hughes [2,11], length at birth, weight at birth, and occipitofrontal circumference (OFC) are 3.2, 1, and 1.8 standard deviations above the mean, respectively. Almost 76 percent of the one hundred and seven cases of Sotos syndrome reported by Tatton-Brown stated the birth weight of the infants in this syndrome to be less than the 98th percentile

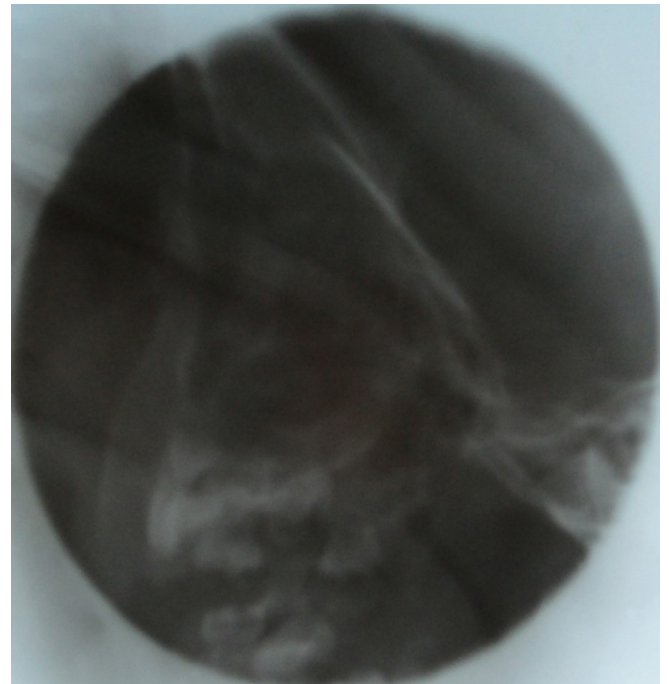


Fig 5. Extraoral radiograph revealing absence of significant number of his teeth and very few tooth buds were visible

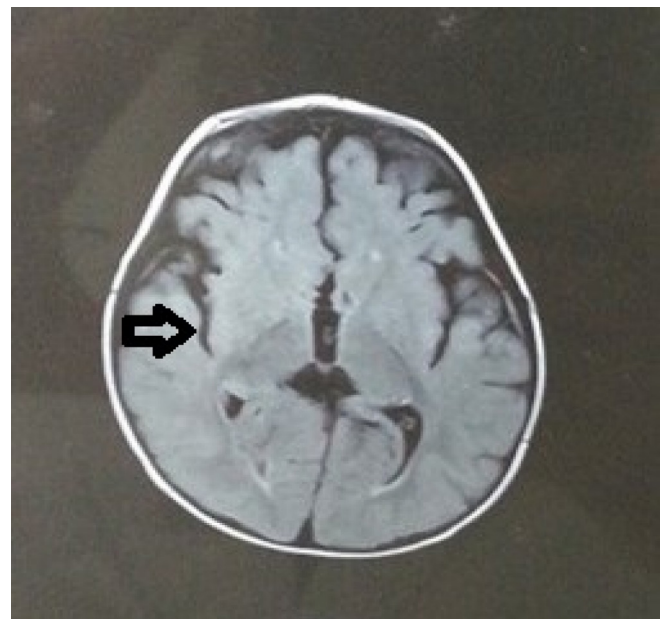


Fig 6. MRI revealing cortical displacement. The indentations are more than what is usually present in a child of age 3-4 years

[2,13]. Many infants have experienced early feeding difficulties and some even require tube feeding. They also show variable degree of congenital hypotonia, jaundice by hyperbilirubinemia or hypoglycemia. The advance growth is primarily conspicuous in the first year of life. It stabilizes during two to six years of age. The height and the weight tend to become normal during the time of puberty. This normalcy at puberty in these individuals can be attributed to the fusion of the epiphysis. Final height is within the

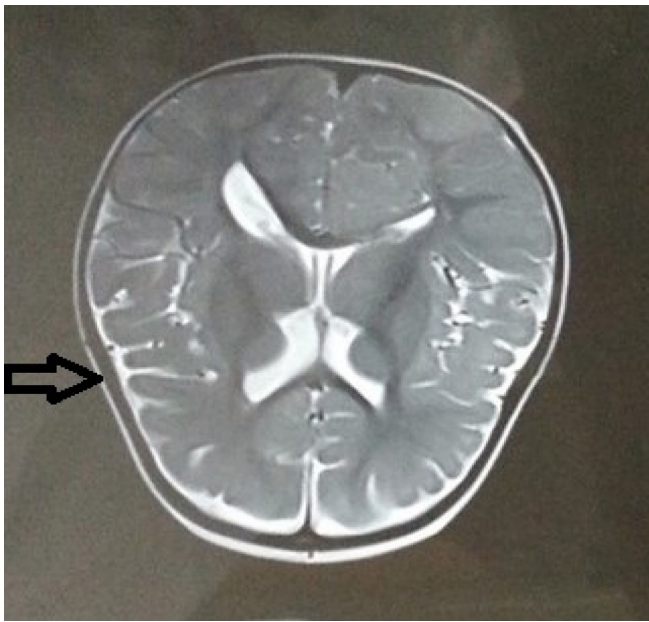


Fig 7. MRI showing decreased periventricular white matter



Fig 8. MRI showing Corpus callosum of apparently normal size

high normal range in most of the patients, particularly females because the growth pattern begins to correlate quite well with the existence of advanced bone age and early puberty. Constant features of this syndrome include macrocephaly, large hands and large feet. Premature fusion of coronal, sagittal and lambdoid sutures has been documented leading to craniosynostosis [2].

Between one and six years of age features are very typical. The face of the infant is usually round with disproportionate prominence of the forehead. The face becomes longer with

prominent pointed chin during adolescence. Receding hairline, macrocephaly, dolichocephaly, micrognathia, hypertelorism, down slanting palpebral fissures, prominent jaw, malar flushing, anteverted nostrils, large ears and high arched palate are commonly seen [2]. Apart from these typical features that have already been reported, our case showed features like elongated face, sparse eye brows, low set large ears, sunken eyes, bilateral divergent squint, depressed nasal bridge, prominent jaw, malar flushing and mild micrognathia at the age of 4 years.

Neurological dysfunction that is usually non-progressive is seen characterised by reduced coordination and clumsiness. During childhood there will be language and motor developmental delay. The learning disability has variable degree. Commonly recognised and familiar feature is the delay in walking until the child reaches fifteen months of age and delay in speech until two and a half years of age. Febrile seizures are seen in more than half of the children [2]. In our case, when the child was one year old he had developed seizures. Milestones like walking, speech were delayed and the patient had poor concentration abilities. The parents also reported that they experienced feeding difficulties, constant episodes of fever, and that the child gets agitated very fast.

Cerebral ventricle dilation, absence of corpus callosum, cortical sulcus that are very prominent, cavum septum pellucidum and cavum velum interpositi are other features that may be seen [2]. In our case, MRI revealed cortical displacement and decreased periventricular white matter.

Dental care in such children are very complicated and problematic due to the child's intellectual inadequacies, reduced communication skills and diminished capability to comprehend simple techniques. Hence, the oral health management for such individuals focuses mainly on prevention. Their lack of ability to mechanically remove plaque increases their caries predisposition. The parents or guardians of specially abled individuals must understand that there is a need for both the family and the dental professionals to act together so as to have a combined effort and methodically supervise the oral hygiene to improve the oral health status [7]. In our case too, the patient was referred to the paediatrician and craniofacial surgeon for consultation. Oral hygiene instructions and counselling on dietary habits were given to the parents.

Jaundice during neonatal period can be treated by phototherapy as done in our case. Alterations in baby food to aid in swallowing may be considered. Adaptations such as eating upright and elevating the head of the bed to avoid gastroesophageal reflux, heartburn and vomiting may be useful. Periodic follow-up and recall with the paediatrician is necessary, to attend to problems like constipation, respiratory infections, seizures and also due to the increased risk of tumor development in the near future [2,15]. Comprehensive treatment with preventive measures, restorations and extractions as well as education and motivation of parents to maintain oral hygiene

and visit dental surgeon for periodic recall and check-up is required [1]. We have also taken a comprehensive approach to treat our case. After due consultations with the craniofacial surgeon and the paediatrician, the restorative/rehabilitative treatment are being carried out at subsequent appointments.

CONCLUSION

Medical problems, disabilities and limitations of children with special needs are very demanding as well as challenging. The general attitude of the public and society does not consider oral health care of such patients a priority. Parents of such children must be advised that neglecting daily oral hygiene can lead to dental problems which can cause discomfort and pain, and which may have adverse systemic consequences for their children. Patient and parents must be educated and motivated for a comprehensive treatment approach of such children.

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