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PROGRESSIVE NON-INFECTIOUS ANTERIOR VERTEBRAL FUSION IN A BABY WITH SAETHRE-CHOTZEN-ACROCEPHALOSYNDACTYLY TYPE III SYNDROME

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We report on a 3-months old baby of Austrian origin and product of non-consanguineous parents. Abnormal craniofacial contour was the main deformity. The overall clinico-radiographic features were consistent with Saether-Chotzen-acrocephalosyndactyly type III syndrome. Bi-directional sequencing of the exon 8 and of the FGFR3-genes, exons 7 of FGFR3 (Fibroblast growth factor receptor3) genes, the exon 5 of the FGFR1 gene, revealed no mutations. Sagittal MRI imaging of the spine showed anterior vertebral fusion along the thoraco-lumbar vertebrae compatible with the non-infectious type.

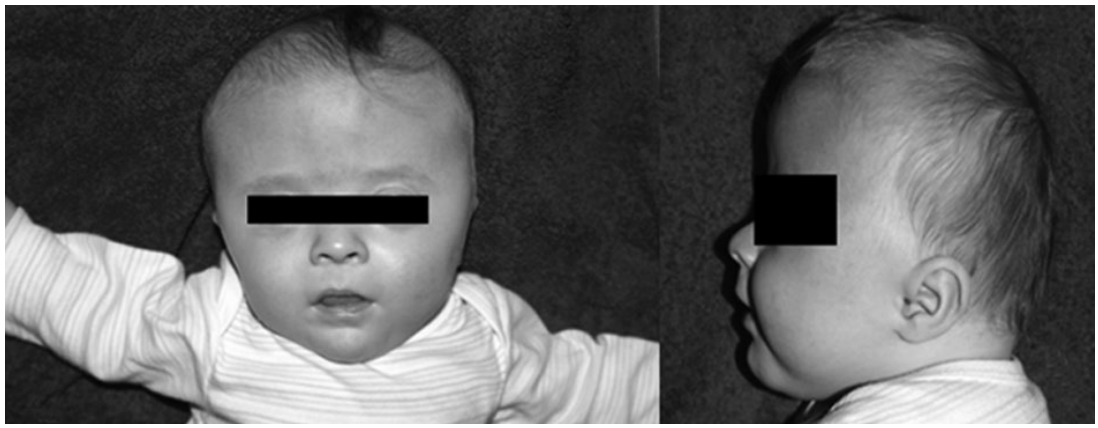
Keywords: Saethre–Chotzen syndrome; FGFR3-genes; Progressive non-infectious anterior vertebral fusion; MRI.

Introduction

Saethre-Chotzen syndrome, also known as acrocephalosyndactyly type III (ACS III) is a very rare congenital syndrome characterized by craniosynostosis (premature closure of one or more of the sutures between the bones of the skull) .It is characterised by asymmetric facies, brachycephaly, parietal foramina, a broad forehead, ptosis, a beaked nose, loss of the frontonasal angle, low-set ears with folded pinnae and prominent cruri, and minor abnormalities of the hands and feet. The latter consist of soft tissue syndactyly, mild brachydactyly, clinodactyly and hallux valgus. The hallux can be quite broad but is not in varus as seen in Pfeiffer syndrome [1, 2, 3]. The early radiological changes in patients with anterior vertebral fusion are characterised by a narrowing of the anterior part of disc space with progressive erosions of the adjacent vertebral end plates. In most instances, the posterior part of the disc is not affected at this early stage. The narrowing progresses to obliterate the disc space anteriorly, with eventual bony ankylosis. When new bone formation accompanies the erosive changes, the ankylosis occurs as a bony ridge. A large series of 80 cases including patients from the university Hospital of Copenhagen was published [4, 5]. This spine pathology develops shortly after birth, and the progressive fusion in the thoraco-lumbar spine results in an acutely angled kyphosis. The aetiology is unknown.

Case report

A-3-months old baby male has been referred to our department for clinical evaluation. He was a product of full term uneventful gestation. At birth his weight, length and OFC were around the 10 th percentile. Bilateral coronal sutural synostosis has been observed with subsequent development of brachycephaly. External ear malformation manifested as posteriorly rotated ears with low setting and prominent helical crura were noted. Hypertelorism, a broad mid-face, beaked nose, a high arched palate with no clefting was present. Bilateral epicanthal folds associated with downward slanting of the palpebral fissures were evident (fig 1, A, B). Mild syndactyly of the second and third interdigital spaces of the fingers, clinodactyly of the 5 th fingers, and cutaneous syndactyly of the toes 2 and 3 respectively, associated with a broad hallux. MRI imaging showed no Chiari-malformations and or syringomyelia (fig 2). But, nevertheless, progressive non-infectious anterior vertebral fusion was the



A B

Fig. 1 (A, B) Craniofacial phenotype showed wide frontal area in connection with bilateral coronal sutural synostosis were identified with subsequent development of brachycephaly. External ear malformation manifested as posteriorly rotated ears with low setting and prominent helical crura were noted. Hypertelorism, a broad mid-face, beaked nose, a high arched palate with no clefting was present. Bilateral epicanthal folds associated with downward slanting of the palpebral fissures were evident

major orthopaedic abnormality. Sagittal MRI imagings showed apparent narrowing of the anterior disc spaces with approximation of the anterior corners of the vertebral bodies along T9/L3 associated with adjacent end-plate erosions causing effectively the development of intervertebral bridging (fig 3). Neurological examination was normal. Hearing, vision and intelligence were normal as well. Parameters of blood biochemistry were normal. Bi-directional sequencing of the exon 8 and of the FGFR3-genes, exons 7 of FGFR3 (Fibroblast growth factor receptor3) genes, the exon 5 of the FGFR1 gene, no mutations have been encountered. Mutations of TWIST gene have not been investigated. Multiple staged surgeries are the general treatment plan for patients with Saethre-Chotzen syndrome. In the first year of life it is preferred to release the synostotic sutures of the skull to allow adequate cranial volume to allow for brain growth and expansion. This procedure may need to be repeated in the life of the child. In addition, depending on the severity of the skull deformity, this procedure may be done in one stage or two stages.

Discussion

SCS belongs to agroup of autosomal dominant craniosynostosis syndromes that have several clinical features in common and diagnostic dillema continue to arise, with single cases being particularly difficult to classify. The most commonly used classification for craniosynostosis is based on the shape

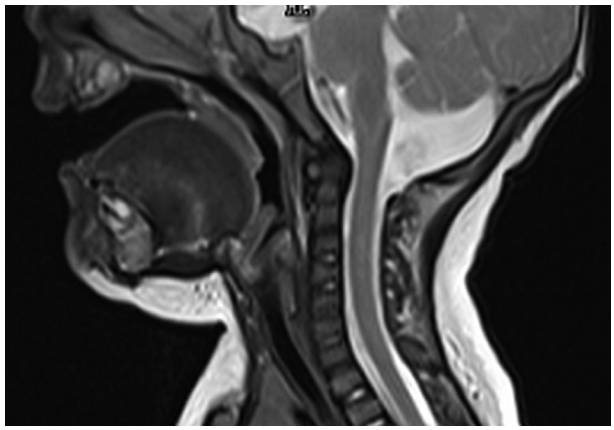


Fig. 2. Sagittal MRI imaging of the craniocervcial region showed no Chiari-malformations and or syringomyelia

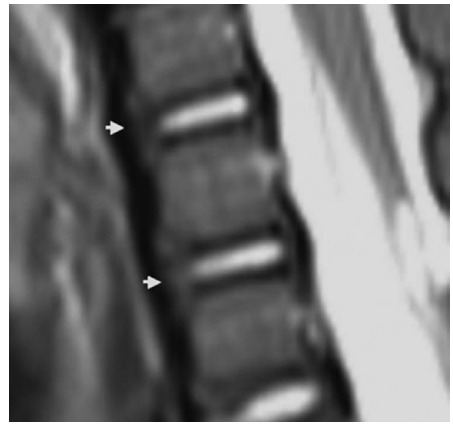


Fig. 3. Sagittal MRI imaging showed apparent narrowing of the anterior disc spaces with approximation of the anterior corners of the vertebral bodies along T9/L3 associated with adjacent end-plate erosions causing effectively the development of intervertebral bridging

of the skull, which reflects the underlying prematurely closed sutures. SCS is a form of acrocephalosyndactyly It is characterised by asymmetric facies, brachycephaly, parietal foramina, a broad forehead, ptosis, a beaked nose, loss of the frontonasal angle, low-set ears with folded pinnae and prominent cruri, and minor abnormalities of the hands and feet. The latter consist of soft tissue syndactyly, mild brachydactyly, clinodactyly and hallux valgus. The hallux can be quite broad but is not in varus as seen in Pfeiffer syndrome [1, 2, 3, 6, 7]. Craniosynostosis and Saethre-Chotzen syndrome may be unicoronal or bicoronal; metopic suture fusion is found in some cases, but sagittal suture fusion is rare. Most patients with SCS however, have been demonstrated to harbour a mutation in the TWIST gene. Some patients with an overlapping phenotype have mutations in the FGFR3 gene. Patients with Muenke syndrome may resemble patients with SCS to a great extent. Significant interfamilial phenotypic variability is present for the TWIST mutation. The detection rate for TWIST mutations in patients with SCS is approximately 68% [8]. Previous reports described the associated malformation complexes in patients with (SCS). Aase and Smith [9] described a syndrome comprising asymmetry of the face (hypoplasia of the left side), unusually shaped ear with prominent crus, and simian crease in 5 members of 3 generations (with 1 instance of male-to-male transmission). They pointed out similarities to and differences from the asymmetry of the face and skull with abnormalities of the digits described by Waardenburg et al. [10]. Sahlin et al [11], found that 15 (52%) of 29 women over the age of 25 with Saethre-Chotzen syndrome from 15 families developed breast cancer. At least 4 patients developed breast cancer before age 40, and 5 between 40 and 50. The authors concluded that breast cancer is a previously unrecognised symptom of the disorder and further suggested that the TWIST1 gene may be a breast cancer susceptibility gene. Anderson et al described various vertebral fusions in patients with SCS [12].

Vertebral fusion disorders are found in many disorders such as mucopolysaccharoidosis [13], Congenital blocked vertebrae [14]. Our patient manifested distinctive spinal maldevelopment resulted from progressive non-infectious anterior vertebral fusion (PVAP) along the thoraco-lumbar vertebrae. The narrowing process had progressed causing obliteration of the disc space anteriorly with eventual bony ankylosis. The development of acute-angled kyphosis is a highly likely outcome due to cessation of anterior growth at the involved level. In most instances the etiology behind PAVP is unknown. Though there were some reports connected PAVP with syndromic association [15].

The resultant acute-angled kyphosis in patients with PAVP tends to progress rapidly during late childhood/ early adolescence. Bracing, appears to reduce and sometimes even reverse the kyphotic deformity. Treatment and follow-ups is mandatory since once there is fusion of all the involved disc spaces, the deformity does not appear to alter.

Conclusion

Syndactyly of digits two and three of the hand and duplication of the distal hallux are variably present in patients with Saether-Chotzen (SC) syndrome. Segmentation defects of the vertebral column have been considered as a less common manifestation in patients with SC syndrome. In general, progressive non-infectious anterior vertebral fusion develops in early childhood and has been reported in infants with no syndromic association (Copenhagen syndrome). Acute-angled thoraco-lumbar kyphosis is the usual orthopaedic presentation. Progressive loss of motor function associated with dreadful neurological deficits might be the outcome.

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ПРОГРЕССИРУЮЩАЯ КОНКРЕСЦЕНЦИЯ ТЕЛ ПОЗВОНКОВ НЕИНФЕКЦИОННОГО ГЕНЕЗА У ПАЦИЕНТА С СИНДРОМОМ SAETHRE-CHOTZEN (АКРОЦЕФАЛОСИНДАКТИЛИЯ III ТИПА)

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В статье описывается клинический случай заболевания трехмесячного ребенка из австрийской семьи от не состоящих в кровном родстве родителей. Основная деформация у пациента — аномальная форма черепа. Общие клинико-рентгенологические признаки соответствуют акроцефалосиндактилии III типа (синдрома Saethre-Chotzen). При секвенировании экзона 8-го гена FGFR3 (рецептор фактора роста фибробластов 3), экзона 5-го гена FGFR1 мутаций не выявлено. При МРТ позвоночника выявлена аномалия развития — конкресценция тел позвонков.

Ключевые слова: синдром Saethre-Chotzen, акроцефалосиндактилия.

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