Saethre-Chotzen syndrome: Case report and literature review

Zespół Saethrego-Chotzena – opis przypadku i przegląd piśmiennictwa

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Abstract

Saethre-Chotzen syndrome (SCS) belongs to a group of rare congenital disorders connected with craniosynostosis and syndactyly. The purpose of this paper is to provide a review of the literature, to collect all reported symptoms and to describe the case of an 11-year-old female with SCS. The electronic databases PubMed and Scopus were searched to gain all symptoms of SCS described in the literature. The most common features of SCS described in the literature are synostosis of the coronal suture, syndactyly, facial asymmetry, low hairline, prominent ear crus, prominent nasal bridge, eyelid ptosis, and ocular hypertelorism. Less common symptoms include hearing loss, renal abnormalities and cardiac defects. Intraoral manifestations of SCS include maxillary hypoplasia, mandibular prognathism and high arched palate. Moreover, in some patients mental disability is observed, which may be connected with the size of the deletion in the *TWIST* gene. There are no pathognomonic symptoms of SCS, which would indicate a diagnostic problem. Our patient displayed small dysmorphic changes within the skull and limbs and proper intellectual development. On the basis of an intraoral, extraoral examination and X-rays, she was diagnosed with relative mandibular prognathism. Currently, she is treated with a removable appliance. This report emphasizes a considerable variability of symptoms in SCS and highlights the most common features.

Key words: craniosynostosis, Saethre-Chotzen syndrome, acrocephalosyndactyly, acrocephalosyndactyly type 3

Słowa kluczowe: kraniosynostoza, zespół Saethrego-Chotzena, akrocefalosyndaktylia, akrocefalosyndaktylia typu III

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Introduction

Saethre-Chotzen syndrome (SCS) (MIM 101400) belongs to a group of rare genetic disorders known as acrocephalosyndactyly, which is characterized by syndactyly and craniosynostosis – the premature fusion of certain cranial sutures.[1,2] Craniosynostosis can be a part of a genetic syndrome (e.g., Apert, Crouzon, Pfeiffer, SCS) but more often it is an isolated defect – approx. 85% of all craniosynostosis cases are nonsyndromic.[2]

Saethre-Chotzen syndrome is one of the most common craniosynostosis syndromes and was first described independently by 2 psychiatrists: Haakon Saethre (1931) and Fritz Chotzen (1932) as acrocephalosyndactyly type 3.[2] The prevalence of SCS is estimated at 1/25000 to 1/50000 of live births.[3] Saethre-Chotzen syndrome may often go unrecognized, especially in the group that does not experience craniosynostosis and that is the reason why the real number of cases may be higher than estimated.[2,4] It affects both sexes equally.[5]

Gene mutations were proved to be responsible for SCS – mainly modifications in the *TWIST1* gene of chromosome 7p21, containing the bHLH domain, which is important for the development of the head and limbs and is inherited in an autosomal dominant manner.[2,6] Rarely, it may also be caused by FGFR2 and FGFR3 gene mutation.[7] However, occurrences of the novo mutation are also reported.[1]

The characteristic of SCS includes a premature closure of cranial sutures, particularly the coronal suture, which usually begins within the first 12 months of life. This coexists with finger and/or toe abnormalities. Coronal synostosis occurs in 20–30% of all craniosynostosis cases with females being more often affected than males.[2,8,9] Intraoral manifestations of SCS include maxillary hypoplasia, mandibular prognathism, and high arched palate.[2]

The aim of this study is to present a case report of a 9-year-old girl with SCS treated in our clinic and to emphasize the wide variability in the phenotypic expression of this syndrome on the basis of literature review.

Case report

A 9-year-old female was referred to the Department of Orthodontics, Division of Facial Abnormalities (Wroclaw Medical University, Poland) by a general dentist who was concerned about her malocclusion.

According to the medical history, the girl was born in a natural way after 40 weeks of gestation with a birth weight of 3180 g. This was the mother's 3rd pregnancy and the 1st that was full-term. After birth, apart from the features of craniofacial dysmorphism, she was diagnosed with cyanosis, reduced muscle tension, and poor reflexes. Moreover, the girl required pneumonia, respiratory and renal failure treatment shortly after labor. Advanced care was provided and she had been under the care of numerous specialists since she was a neonate: cardiologist due to congenital valvular pulmonary stenosis and interatrial septal defect, endocrinologist because of hypothyroidism and ophthalmologist due to divergent strabismus and myopia. There was no family history of acrocephaly. The parents underwent a genetic test that showed a correct karyotype, indicating that SCS was caused by de novo mutation in the *TWIST1* gene.

A general examination revealed features of craniosynostosis and face dysmorphic traits, such as a broad forehead with low hairline, hypotelorism, a "beaked" nose with a depressed nasal bridge, and small low-set ears. The profile of the patient is straight with the light retrusion of the chin (Fig. 1). Finger abnormalities were also present in the form of brachydactyly with a significant shortening of the little finger and nail dysplasia (Fig. 2).

Intraoral examination revealed a high arched palate, crowding in the upper and lower arch, angle class I on both sides, canine class I on the right side, class II on the left side, and a dual tooth 12. The midline of the lower arch was shifted to the left side and mixed dentition was observed. The deciduous canine, molars, permanent incisors, and first molars in the upper and lower arches were present, which is correct for the patient's age (Fig. 3). In the 1st step of diagnostic imaging, an orthopantomo-

Fig. 1. Extraoral photographs

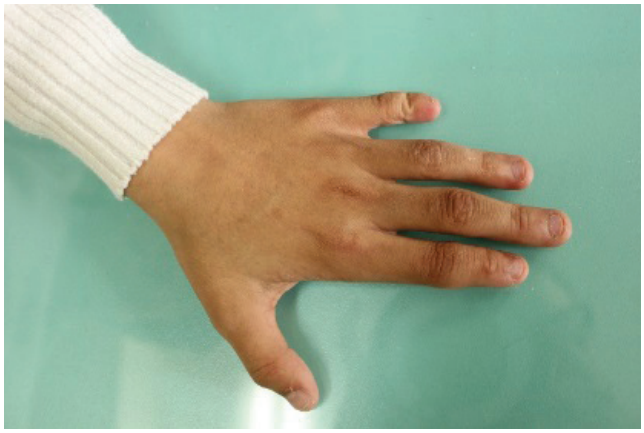

Fig. 2. Fingers abnormalities

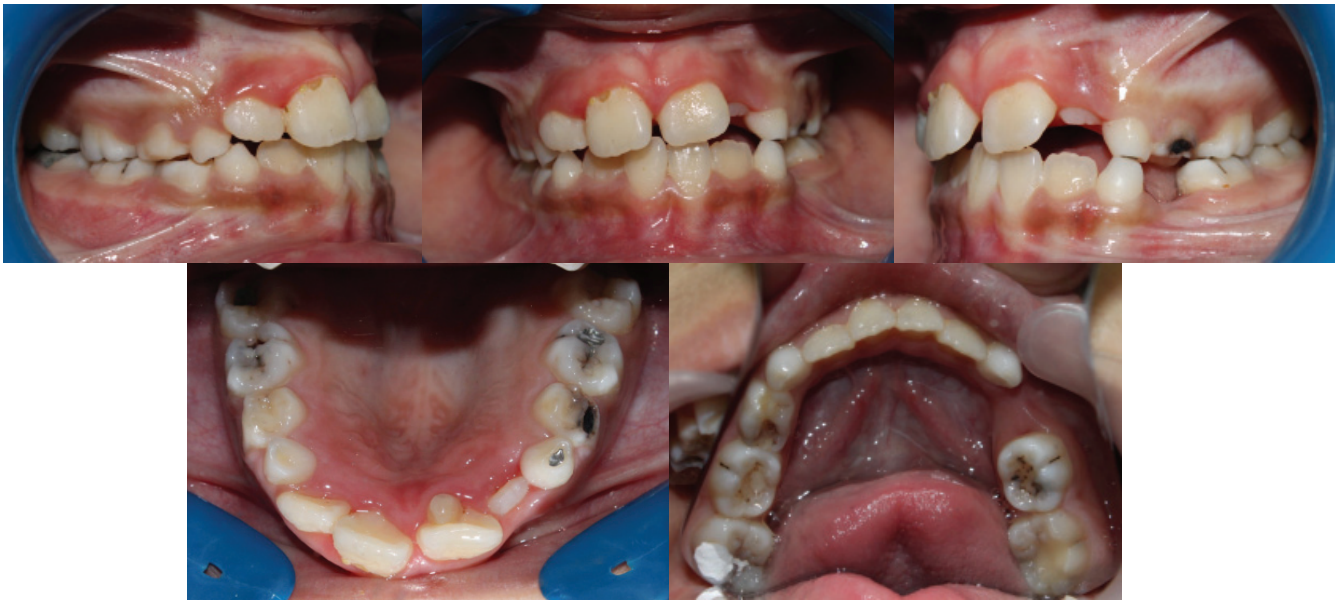

Fig. 3. Intraoral photographs

graph evaluation (Fig. 4) was performed and it demonstrated the presence of all permanent teeth. Poor oral hygiene and severe decay are observed. The calculated DMFT index was 12 indicating the need for conservative treatment of the patient. The cephalometric analysis verified maxillary retrognathia (SNA = 73.0°), mandibular retrognathia (SNB = 75.9°), skeletal class III malocclusion (ANB = –2.5°), which confirmed relative mandibular prognathism (Fig. 5, Table 1)

A physical examination confirmed by a radiological X-ray showed a lack of the coronal suture. The psychological examination revealed hyperactivity, with no abnormalities in intellectual development. The mother reported that the girl removed her hair excessively, which was confirmed by a bald spot on her head (Fig. 1). Further genetic diagnostics are planned. The diagnosis was performed on the basis of clinical features.

Table 1. Cephalometric measurements of 11-year old patient

Description	Cephalometric measurements	Value	Mean	SD
Maxilla to cranial base	SNA	73.0°	82.0°	±3.0°
	NL-NSL	9.5°	8.0°	±4.0°
Mandible to cranial base	SNB	75.9°	80.0°	±3.0°
	ML-NSL	40.7°	28.0°	±5.0°
Maxilla to mandible	ANB	–2.0°	2.0°	±2.0°
	wits	–4.6°	0°	±2.0°
	ML- NL			
Maxillary dentition	U1-NA [mm]	8.0°	3.7°	±2.0°
	U1-NA	30.0°	21.0°	±4.0°
Mandibulary dentition	L1-NB	3.1°	3.8°	±5.0°
	L1-NB	23.8°	24.0°	±4.0°
Soft tissue	naso-labial angle	104.4°	110.0°	±7.0°

SD – standard deviation.

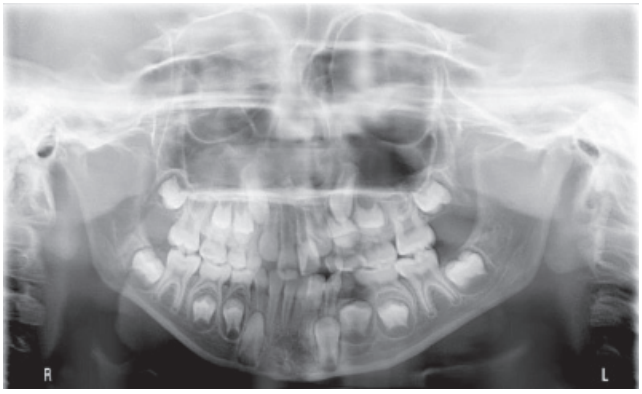

Fig. 4. Orthopantomograph

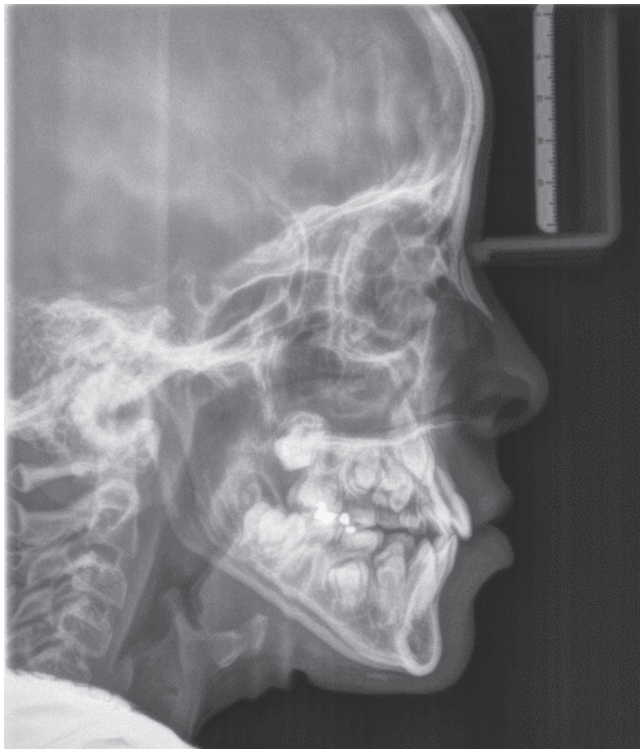

Fig. 5. Lateral cephalometric radiograph

Table 2. Systematic review from 2000 to 2017

Article	Publication type	A	Details about patients	Genetic confirmation	B	C	D	E	F	G	Conclusion
Shimbo et al., 2017[10]	case report	1	15-month-old male	de novo 0.9-Mb microdeletion in 7p21	–	–	+	+	+	–	HDAC9 was suggested to contribute to developmental delay in SCS patients with 7p21 microdeletions
Mitsukawa et al., 2016[11]	case report	4	4-year-old male	mutation in the *TWIST* gene, 445C> T	+	+	0	+	–	–	familial case report of 4 individuals with SCS of 3 generation and surgical management of brachycephaly and blepharoptosis in these patients
			11-year-old male		+	+	0	+	–	–	
			45-year-old female		+	+	0	–	–	–	
			72-year-old female		0	+	0	–	–	–	
Tahiri et al., 2015[12]	case report	5	7-year-old female	duplication of 21 bp from nucleotide 396 to 416 of the *TWIST* gene resulting	0	+	–	0	–	–	new and unique pattern of sutural fusion "peace sign synostosis" (PSS) characterized by synostosis of the metopic, bicoronal and sagittal sutures
			13-month-old male	8.72Mb de novo deletion in 7p21.2p15.3	0	+	–	0	–	–	
			18-month-old male	I point mutation in the *TWIST* gene c.421 G → A	0	+	–	0	–	–	
			9-month-old male	12Mb 7p21.1:7p15.1 deletion	0	+	–	0	–	–	
			10-month-old male	1.0Mb interstitial deletion of 7p21.1 240 kb away from the *TWIST* gene	0	+	–	0	–	–	
Di Rocco et al., 2015[13]	case report	1	22-month-old male	0	–	+	+	–	–	–	case of a patient with complex craniosynostosis with a unique antenatal progressive fusion of both coronal sutures and of the metopic suture with an absence of mental retardation
Shimada et al., 2013[14]	case report	1	5-year-old male	microdeletions in 4q13.2 and 7p21.1	–	+	–	+	–	–	case report of the patient with a typical SCS phenotype and additional severe neurological features
Cho et al., 2013[15]	case report	1	16-month-old boy	deletion of 148 kb, involving *TWIST1*	–	+	–	+	–	–	author emphasizes important contribution of array CGH to the identification of *TWIST* microdeletions, even in a patient not showing the phenotype typical of SCS
Zechi-Ceide et al., 2012[16]	case report; research support	1	15-year-old female+	7p21 and 3p21.31 microdeletions	+	+	+	+	–	–	patient displays clinical findings that fit into both diagnoses: SCS and hyper IgE syndrome
Spaggiari et al., 2012[17]	case report	1	23 weeks of gestation	11.4 Mb deletion from nt 17,042,756 to nt 28,469,318 in chromosomal region 7p15.1-p21.1.	–	+	+	0	–	0	first prenatal case of a de novo molecularly well delineated *TWIST1* gene deletion associated with SCS. The pregnancy was terminated
Fryssira et al., 2011[18]	case report	1	newborn boy	microdeletion on chromosome 7p21.1–p14.3 detected by array-CGH and encompassing the *TWIST* and *HOXA* gene cluster	–	+	+	0	+	–	patient with a combined phenotype of SCS and hand-foot-uterus syndrome. Deletion encompassed 74 genes and caused haploinsufficiency of 6 genes known to be implicated in different autosomal dominant genetic disorders: *TWIST, DFNA5, CYCS, HOXA11, HOXA13,* and *GARS*
De Jong et al., 2011[19]	research support	21	0	0	0	0	0	0	0	0	moderate hearing loss was diagnosed in 28.6% of patients with SCS
Rosen et al., 2011[20]	comparative study	29	12 males	0	62% +						most patients with SCS suffered from hearing loss at some point during their childhood, but it usually resolved. Research shows that 59% of patients had at least 1 abnormal audiogram, but 72% had normal hearing on their last audiogram
			17 females	0	38% –	0	0	0	0	0	
			from 0.7 to 24.5 years	0							
De Marco et al., 2011[21]	case report; research support	1	5-year-old female	de novo balanced translocation 46, XX, t(7;12)(p21.2;p12.3	–	+	–	–	–	–	confirmatory case report providing further evidence for *TWIST1* haploinsufficiency in SCS, and a possible role of PTP-oc as a genetic factor underlying or at least influencing the development of craniosynostosis
Busche et al., 2011[22]	case report; research support	3	2-year-8-month-old female	11.7Mb deletion in the 7p21.2p15.2	–	–	+	+	–	–	clinical manifestations of SCS depend of the deletion size
			1-year-8-month-old female	526 kb deletion in the 7p21.1	0	–	–	–	–	–	
			16-year-old male	9.2 Mb deletion in the chromosomal region 7p15.2p21.1	0	+	+	+		hypo-dontia	
Lamônica et al., 2010[23]	case report; research support	3	45-year-old female (mother) 14-year-old male (son) 12-year-old female (daughter)	Pro136His mutation	+	+	+	+	–	–	report suggests that there may be a correlation between Pro136His mutation and hearing loss in a patient with SCS
Foo et al., 2009[24]	case report	22	birth – 32-year-old	23% complete deletions of the *TWIST1* gene; 77% unique missense, nonsense, insertion, or intragenic deletion mutation of the TWIST1 gene.	0	+	+	+	+	–	different locations of the *TWIST1* gene mutation in this study did not correlate to a specific surgical outcome
De Jong et al., 2009[25]	research support	35		0	0	0	0	0	0	0	refractive error 14 of 27 (52%); strabismus 13 of 35 (37%); impaired hearing 35 (37%); OSA 2/38 5%
Peñ et al., 20092[6]	case report	1	3-week-old female	novel sequence variant, c.G572T, predicting p.R191M in the *TWIST* 1 gene	+	+	+	+	–	–	case report of a girl with clinical features of SCS who has a previously undescribed sequence variant in the *TWIST1* gene, corresponding to p.R191M
Stoler et al., 2008[27]	case report; comparative study	51		0	0	0	0	0	0	0	high-arched palate in 43%, bifid uvula in 10%, cleft palate in 6%
Schlut-Bolard et al., 2008[28]	case report; research support	1	4.5-year-old male	translocation between the short arms of chromosomes 2 and 7 and an insertion of the 7(q21.3q22) 690 kb deletion in 7p21.3 involving the *TWIST* gene	–	+	+	+	–	–	case report of a patient with characteristic features of SCS diagnosed by array CGH
Raybud et al., 2007[29]	review	2	6 years; 14 years	0	0	0	0	0	0	0	neurological non-specific finding about the presence of a mega cisterna magna and poor contrast for age between the grey and white matter
Shetty et al., 2007[30]	research support	1	female infant	translocation between chromosomes 7 and 18 46,XX,t(7;18)(p15.3;q11.2); interstitial 7.6–10.6-Mb deletion of the region between bands 7p21.2 and 7p21.3 on the derivative chromosome 18.	–	+	+	+	–	–	patient with a complex mutation of genes and serious symptoms of SCS
Seifert et al., 2006[31]	case report	1	5-year-old female	a new stop mutation (c.570GOA; p.Trp190X) and a known missense mutation (c.379GOC; p.Ala127Pro) in	–	+	+	–	–	–	case of a patient with SCS associated with metastatic renal cell carcinoma originating in the right kidney
Lopes Burrone De Freitas et al., 2004[32]	research support	24	0	Q289P mutation in the FGFR2; 3/24	+	24/24	24/24	2/24	–	–	case report of 4 families suffering from SCS
De Heer et al., 2004[33]	case report	13	0	small mutation in *TWIST* gene	+	2/13	12/13	0/13	0	0	a large 5-generation family with characteristics of SCS
Chun et al., 2002[34]	research support	11	1–13 years old	mutation in *TWIST* gene 2/11	1/2	1/2	1/2	0/2	–	–	initial screening for the FGFR3 P250R mutation, followed by sequencing of *TWIST* and then fluorescence in situ hybridization (FISH) for deletion detection of *TWIST*, is sufficient to detect mutations in >80% of patients with the Saethre-Chotzen phenotype
			7 females	deletion in *TWIST* gene 3/11	1/3	3/3	2/3	3/3	0	0	
			4 males	no mutation 6/11	2/6	6/6	3/6	1/6	0	0	
Dollfus et al., 2002[35]	research support	16		0	+	4/16	3/16	0	–	–	4-generation Indian family
Lee et al., 2002[36]	case report; review	1	18-month-old male	*TWIST* mutation	–	+	+	–	–	–	patient with a severe profound sensorineural hearing loss
Boeck et al., 2001[37]	case report	2	7-year-old male female (mother)	11 bp deletion in *TWIST* gene	+ –	+ –	– –	+ –	– –	– –	combination of SCS and rare primary immunodeficiency in a 7-year-old boy

+ present ; – absent; 0 no information. SCS – Saethre-Chotzen syndrome. A – No. of patients; B – family history; C – craniosynostosis; D – limb abnormalities; E – mental retardation; F – cleft; G – dental abnormalities.

Currently, the patient is under the care of our clinic and is treated with a removable expansion appliance – a Schwartz plate with a Fischer screw, which is activated once every 2 weeks (Fig. 6).

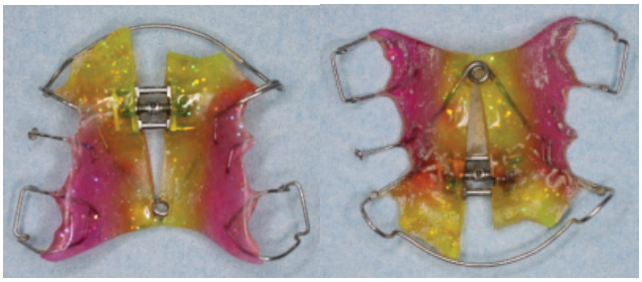

Fig. 6. Schwartz plate

Literature review

The electronic databases – PubMed and Scopus were searched from years 2000 to 2017. The language of the articles was restricted to English. The following keyword was used for the search: "Saethre-Chotzen syndrome". 170 articles from PubMed, 199 articles from Scopus were initially included in the study. Then, references of the articles were searched manually. The inclusion criteria were as follows: case reports with described features of the syndrome in detail; articles on the frequency of occurrence of a particular feature, review of the literature focused on SCS. The exclusion criteria: not enough details about the patients, animal studies, studies focused on genetic diagnostic methods (Table 1).

Twenty eight articles[10–39] were finally chosen after applying the selection criteria and removing duplicated papers (Fig. 7, Table 2). The above-mentioned articles, which described more than 10 cases of SCS, were additionally screened to show the frequency of the most common features (Table 3).[24,34,35,38,39]

Discussion

Saethre-Chotzen syndrome belongs to a group of rare genetic disorders known as acrocephalosyndactyly disorders. This genetic condition is characterized by the premature fusion of certain bones of the skull (at 1–3 years of age) and the fusion of certain fingers or toes.[40] The most common is the premature fusion of the coronal suture, which is located between the frontal bone and the parietal bone and is perpendicular to the sagittal suture.[3] These changes can result in various cranial dysmorphologies depending on where the premature closure of the coronal suture occurs: acrocephaly, which includes the premature closure of the coronal sutures alongside any other suture, like the

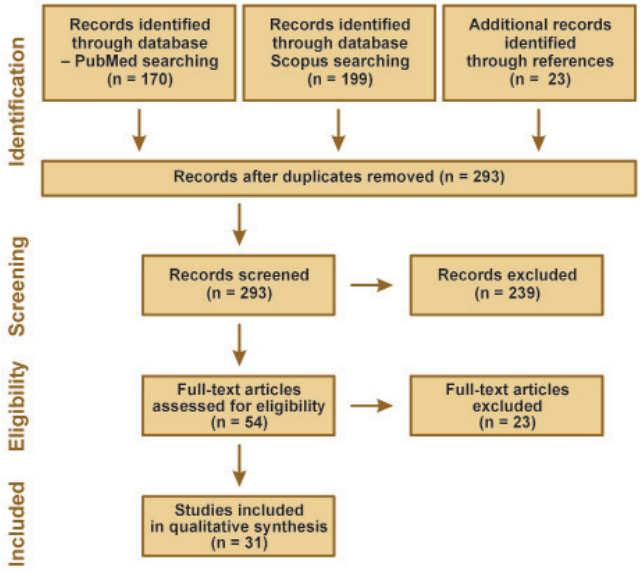

Fig. 7. PRISMA flow diagram
Based on Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

lambdoid, resulting in an abnormally high, peaked, or cone-shaped cranium,[6] and brachycephaly, where the premature fusion of the coronal sutures includes both the right and the left side of the skull.[2] In rare cases, trigonocephaly, cloverleaf deformity, and oxycephaly can also be observed.[4] In some cases the cranial sutures may fuse unequally and thus contribute to facial asymmetry. Asymmetric craniosynostosis is called plagiocephaly and it occurs in approx. 25% of patients suffering from SCS.[4] An early fusion of cranial sutures may lead to increased pressure within the skull (intracranial pressure) and contribute to neurological disorders. According to De Jong et al., SCS is associated with a 21% risk of elevated intracranial pressure (ICP).[25]

Despite the improper shape of the skull, many abnormalities relating to the face may be observed: a broad forehead with a low hairline, small, low-set ear, and many defects of the nose such us a "beaked" nose, deviated nasal septum, and a depressed nasal bridge.

When it comes to the eyes, ocular hypertelorism (widely spaced eyes), unusually shallow eye cavities (orbits), ptosis (drooping or falling of the upper eyelids), and strabismus were observed.[25] Moreover, a nasolacrimal duct stenosis causing decreased tear secretion and susceptibility to eye infections may be presented.[3,41]

Many individuals with SCS demonstrate hypoplastic maxilla and midface hypoplasia with relative mandibular prognathism. Moreover, a highly arched palate may be observed. According to Stoler et al., it occurs in 43% of cases.[27] In rare cases, cleft palate is diagnosed, which is described by Stoler et al. in 6% of patients, while a bifid uvula was observed in 10% of cases.[27]

Table 3. Phenotypic representation

Phenotype	Dollfus et al.[35]	Nascimento et al. [38]	Heer et al.[33]	De Heer et al.[39]	Chun et al.[34]	Foo et al.[24]
Number of patients	16	24	13	32	15	22
Cranial features						
craniosynostosis	25% oxycephaly	–	15%	7	100%	100%
other	–	100% brachycephaly	–	4% brachycephaly	60% brachycephaly	–
Facial asymmetry	N/A	83%	85%	N/A	73%	59%
Ears features						
prominent ears crus	69%	62.5%	69%	56%	N/A	64%
low set ears	N/A	58%	N/A	N/A	20%	N/A
different ears anomalies	37% small ears	42% posterior rotated ears	N/A	N/A	27%	N/A
Maxillary hypoplasia	N/A	54%	N/A	N/A	N/A	0%
Nose features						
prominent nasal bridge	N/A	54%	N/A	65%	N/A	N/A
nasal septal deviation	75%	37.5%	N/A	N/A	N/A	N/A
beaked nose	N/A	29%	N/A	N/A	N/A	
Eyes features						
eyelid ptosis	93%	50%	85%	53%	53%	82%
occular hypertelorism	N/A	46%	23%	N/A	53%	N/A
epicanthus	N/A	17%	8%	N/A	13%	N/A
strabismus	N/A	12.5%	N/A	N/A	20%	27%
ocular hypotelorism	N/A	4 %	N/A	N/A	N/A	N/A
downslanting palpebral fissures	N/A	N/A	15%	N/A	N/A	73%
lacrimal duct stenosis	N/A	N/A	8%	N/A	N/A	N/A
proptosis	18%	N/A	N/A	N/A	N/A	N/A
blepharophimosis	12.5%	N/A	54%	N/A	N/A	N/A
Limbs abnormalities						
cutaneous syndactyly	100%	79%	8%	N/A	27%	27%
clinodactyly	81%	54%	15%	N/A	33%	18%
broad great toes	93%	54%	N/A	N/A	27%	N/A
cutaneous syndactyly of the feet	N/A	37.5	N/A	N/A	N/A	N/A
brachydactyly	100%	25%	69%	N/A	20%	4,5%
single transverse palmar crease	N/A	25%	N/A	N/A	33%	N/A
digit form thumb	N/A	21%	N/A	N/A	N/A	N/A
broad thumb	N/A	8%	N/A	N/A	N/A	N/A
bifid digit externity	18%	N/A	N/A	N/A	N/A	N/A
Other mental retardation	N/A	8%	0%	N/A	27%	27%
Epilepsy	N/A	4%	N/A	N/A	N/A	N/A
High arched palate	69%	N/A	N/A	N/A	N/A	N/A
Lowset hairline	N/A	50%	N/A	56%	27%	63.6
Hearing loss	N/A	N/A	N/A	N/A	33%	27%
Heart defects	N/A	N/A	N/A	N/A	7%	4.5%
Cleft palate	N/A	N/A	N/A	N/A	N/A	14%
Dental malocclusion	N/A	21%	N/A	N/A	N/A	N/A

Dental anomalies in a patient with SCS were reported first by Goho.[42] A characteristic dental feature of this anomaly is the presence of teeth with broad, bulbous crowns, long, narrow tapering roots, and multiple pulp stones in the pulp chambers of all posterior teeth.[42] Moreover, in patient with SCS, we can notice the absence of certain teeth or supernumerary teeth.[40] Unfortunately, 42% of patients with craniosynostosis require restorative treatment, but poor oral hygiene and high plaque accumulation are not connected with the presence of syndactyly.[43] These dental findings may influence dental care for these patients.

The hands and feet may also be affected by SCS. The most common defects are brachydactyly (unusually short digits) and cutaneous syndactyly of certain fingers and toes, which is usually observed between the 2nd and 3rd fingers and 2nd and 3rd toes and, less frequently, from the 2nd to the 4th fingers.[3,41] Less frequent signs include clinodactyly of the 5th fingers (abnormally bent or curved fingers), "finger-like" thumbs and broad, deviating great toes.[38]

The disorder is also associated with musculoskeletal abnormalities including a union or fusion of certain bones of the spinal column within the neck, short stature, an

abnormal fusion of the forearm bones, limited extension of the elbows or knees, short collarbones, and hip deformities.[3,41] Trusen et al. reported that pathognomonic signs in the skeletal system for SCS are a triangular shape of the epiphysis and a duplicated distal phalanx of the hallux.[41]

Less common symptoms of SCS involve hearing loss, kidney abnormalities, and heart defects.[36] In the literature we can observe that SCS is associated with a higher risk of breast cancer.[7] However, James et al.[44] showed that breast cancer risk is not increased in patients with a *TWIST* mutation.

Most people with this condition display normal intellectual development, but mild-to-moderate disabilities are possible. Some authors reported that children affected by SCS suffer from mental disability and exhibit autistic behavior.[45] The literature features some explanations that SCS caused by microdeletion can affect mental disability.[46] It has been described that the deletion of the *TWIST1* gene contributes to significant developmental delay and most patients with intragenic mutation do not show severe developmental delay.[10,45,47] Shimbo et al. suggested that the developmental delay in SCS patients is connected with a mutation of HDAC 9, which is responsible for the regulation of neocortical neuronal development.[10] Fehlow et al.[48] suggested that in patients with SCS, excessive anxiety, obsessions, compulsions, phobias, irritability, and depression may be displayed.

Differential diagnosis

The diagnosis of patients with SCS is difficult, because the symptoms vary to a large extent from person to person, including affected members of the same family. The differential diagnosis includes other syndromes belonging to a group of craniosynostosis, like Crouzon syndrome, Apert syndrome, Pfeiffer syndrome, Antley-Bixler syndrome, Muenke syndrome, Baller-Gerold syndrome, Robinow-Sorauf syndrome. All these syndromes are characterized by the premature fusion of certain bones of the skull during development, which affects the shape of the head and face. The strong correlation between the genotype and phenotype is only observed in Apert syndrome, where 2 mutations in *Ser252Trp* and *P253* are connected with a larger incidence of cleft palate in the 1st mutation and syndactyly in the 2nd mutation. In the other syndromes, the correlations between phenotype and genotype are less clearly marked. The researchers indicate that some craniosynostosis, which differ clinically, may show identical mutations or be allelic diseases.

Conclusions

Saethre-Chotzen syndrome reveals a huge variability of symptoms (Table 3). Depending on the degree of severity, they can be mild, sometimes even undetectable, or very advanced causing numerous physical defects and mental retardation. Patients suffering from SCS require long-term care from many specialists. Our patient exhibited minor dysmorphic changes within the skull and limbs and proper intellectual development, which is the reason why we can identify the severity of her condition as mild. Furthermore, despite the fact that craniosynostosis usually requires a complex orthodontic therapy, only a minor malocclusion and dental abnormalities have been reported in the presented patient.

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