

P R A C E K A Z U I S T Y C Z N E
położnictwo

Prenatal diagnosis of craniosynostosis (compound Saethre-Chotzen syndrome phenotype) caused by a de novo complex chromosomal rearrangement (1; 4; 7) with a microdeletion of 7p21.3–7p15.3, including *TWIST1* gene – a case report

Prenatalnie wykryta kraniosynostoza (złożony fenotyp zespołu Saethre-Chotzen) spowodowana powstałą de novo złożoną translokacją chromosomową (1; 4; 7) z mikrodelecją 7p21.3–7p15.3, obejmującą gen *TWIST1* – opis przypadku

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Abstract

Craniosynostosis (a premature fusion of the cranial sutures) occurs with a frequency of 1 in 2100–2500 births and in over 40% cases is caused by known genetic factors – either single gene mutations or chromosomal rearrangements. Cases caused by complex chromosomal abnormalities are uncommon and likely associated with compound phenotype.

*Saethre–Chotzen syndrome (SCS) [#101400] is caused by *TWIST1* gene haploinsufficiency. Its phenotype includes uni- or bicoronal synostosis, short stature, facial dysmorphism and variable anomalies of the hands and feet. Due to its poor sonographic manifestation a prenatal diagnosis of SCS is challenging.*

*We report a case of a prenatally detected craniosynostosis (compound Saethre–Chotzen syndrome phenotype) caused by a de novo complex chromosomal rearrangement (1; 4; 7) with a microdeletion of 7p21.3–7p15.3, including *TWIST1* gene.*

Key words: **craniosynostosis / *TWIST1* gene / Saethre-Chotzen syndrome (SCS) / compound / complex chromosomal rearrangements / microdeletion / prenatal diagnosis /**

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Streszczenie

Kraniosynostoza (przedwczesne zarośnięcie szwów czaszkowych) występuje z częstością 1 na 2100–2500 urodzeń i w ponad 40% przypadków jest spowodowana przez znane czynniki genetyczne – mutacje pojedynczych genów lub translokacje chromosomowe. Przypadki spowodowane przez złożonymi rearanżacjami chromosomowymi są rzadkie i charakteryzują się złożonym fenotypem.

Zespół Saethre-Chotzen (SCS) [#101400] jest spowodowany uszkodzeniem genu *TWIST1*. Fenotyp zespołu obejmuje zarośnięcie jednego lub obu szwów wieńcowych, niski wzrost, dysmorfizm twarzy i różne nieprawidłowości dłoni i stóp, trudne do uwidocznienia w badaniu ultrasonograficznym, co utrudnia diagnostykę prenatalną SCS.

W pracy prezentujemy przypadek wykrytej prenatalnie kraniosynostozy (złożony fenotyp zespołu Saethre-Chotzen), spowodowanej powstałą *de novo* złożoną translokacją chromosomową (1; 4; 7) z mikrodelecją 7p21.3–7p15.3, obejmującą gen *TWIST1*.

Słowa kluczowe: **kraniosynostoza / *TWIST1* / zespół Saethre-Chotzen (SCS) /
/ złożona translokacja chromosomowa / mikrodelecja /
/ diagnostyka prenatalna /**

Introduction

Craniosynostosis, a premature fusion of the cranial sutures, occurs with a frequency of 1 in 2100–2500 births [1, 2]. Its etiology includes environmental factors – intrauterine fetal constraint caused by primiparity, multiple pregnancy or macrosomia[3], teratogen exposure [4, 5] and genetic factors – either single gene mutations or chromosomal abnormalities [6]. Cases caused by complex chromosomal rearrangements occur very rarely and are likely associated with variable extracranial abnormalities [7, 8].

Saethre-Chotzen syndrome (SCS) [#101400] is caused by *TWIST1* gene haploinsufficiency. Its classic clinical manifestation includes a uni- or bicoronal synostosis, low-set frontal hairline, ptosis, hypertelorism, maxillary hypoplasia with a high arched palate, small ears with prominent helical crura and variable discrete anomalies of the hands and feet like clinodactyly and broad hallux valgus with bifid distal phalanx [9, 10, 11, 12]. Prenatal diagnosis of SCS, due to a poor ultrasound manifestation of its typical features, is challenging.

We report a case of a prenatally detected craniosynostosis (compound Saethre-Chotzen syndrome phenotype) caused by a *de novo* complex chromosomal rearrangement (between chromosomes 1; 4; 7) with a microdeletion of 7p21.3–7p15.3, including *TWIST1* gene, detected in early infancy.

Case report

A 29-year-old primigravida was referred to our Ultrasound Department at 31 weeks due to fetal dysmorphism. Her medical history was unremarkable. There was no history of teratogen exposure. The parents were non-consanguineous and there were no known cases of neonatal deaths, chromosomal abnormalities, genetic syndromes or developmental delays in the family.

The ultrasound examination revealed a viable single male fetus in a right longitudinal cephalic presentation. The fetal biometry indicated 32 weeks of gestation. The anatomy scan revealed an abnormal cranial shape (“a strawberry-shaped head”) and a hypoplastic midface, visualized as well during the next ultrasound examination at 37 weeks (Figure 1). No other abnormalities were detected.

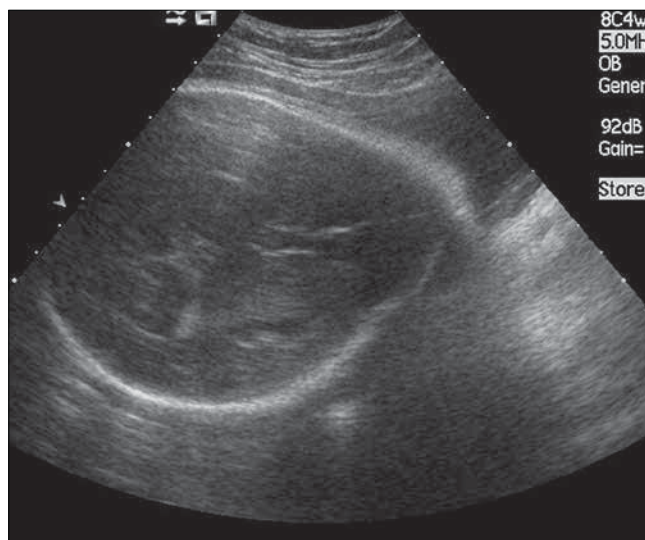


Figure 1. Scan of the “strawberry-shaped” head at 37 weeks.

Fetal karyotyping was performed on the umbilical blood lymphocytes. The standard GTG banding analysis at the 350 band resolution level revealed an apparently balanced complex translocation 46,XY,t(1;4;7)(q42.13;q31.3;p22) (Figure 2). The parental karyotypes, obtained from the peripheral blood lymphocytes, were normal.

A Caesarean section due to a premature rupture of the membranes and a vaginal bleeding from the vasa previa was performed at 38 weeks gestation and a male infant of 3420g was delivered. Apgar score at 1 – 3 – 5 minute was 7 – 7 – 7 respectively. The head circumference was within the normal range – 32 cm.

A generalized hypotonia occurred in the neonatal period. Furthermore, dysmorphic features and extracranial anomalies were observed: a trigonocephaly with prominent metopic suture, large anterior fontanelle, hypoplastic midface with hypotelorism, depressed nasal bridge, high arched palate, ectopic right kidney and a micropenis. No limbs deformities were detected.

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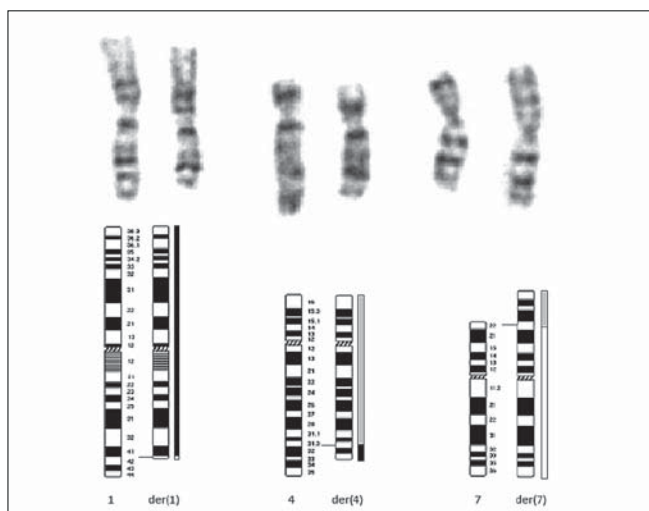


Figure 2. GTG analysis. Partial karyotype of a male fetus with an apparently balanced complex chromosomal translocation 46,XY,t(1;4;7)(q42.13;q31.3;p22).

A three dimensional computed tomography and a magnetic resonance of the head at 3 months of life revealed an asymmetric brain with a broader right lateral ventricle and a deformed skull with craniosynostosis. The metopic suture on the level of the frontal bones and the lambdoidal suture were partially ossified. A large anterior fontanelle was situated centrally and an additional bone was detected in its projection (Figure 3).

Further genetic diagnosis was performed at the age of 2 years by the use of CGX format NimbleGen 12-plex microarray (SignatureGenomicsdesign; manufactured by Roche NimbleGen) with a resolution of 135k (134829 oligonucleotide probes) per each haploid genome. ArrayCGH revealed a pathogenic interstitial deletion of the chromosome 7 (region 7p21.3–7p15.3) of the size of 12.65 Mb – 12.72 Mb (the minimal genomic position according to HG18: 7463949–20108990), that involved 37 genes (Figure 4).

Discussion

The prenatal diagnosis of syndromic craniosynostosis relies mainly on detection of the associated abnormalities and fetal DNA analysis [13]. Poor and variable extracranial manifestation of the classic SCS (broad great toes, clinodactyly) makes its prenatal diagnosis challenging. Despite the fact that the ultrasound examination was proven to be a useful tool to demonstrate the closure of the cranial sutures in the fetuses in the third trimester of pregnancy, cases without familial history are rarely detected prenatally [14].

Only 4 cases of ultrasound prenatal diagnosis of familial SCS have been previously reported in the literature. A family history of the craniosynostosis and an abnormal cranial shape, facial dysmorphism or a visualization of the premature closure of the cranial sutures (at 32 weeks of gestation) led to the appropriate diagnosis [14, 15]. The earliest diagnosis was established at 19 weeks gestation and apart from the irregular shape of the skull, limb abnormalities were present [15].

Galbiati et al. reported in 2013 the first case of a non-invasive molecular prenatal diagnosis of *TWIST1* mutation [16]. However, a non-invasive diagnosis is only applicable to the families with a known high risk of the disease.

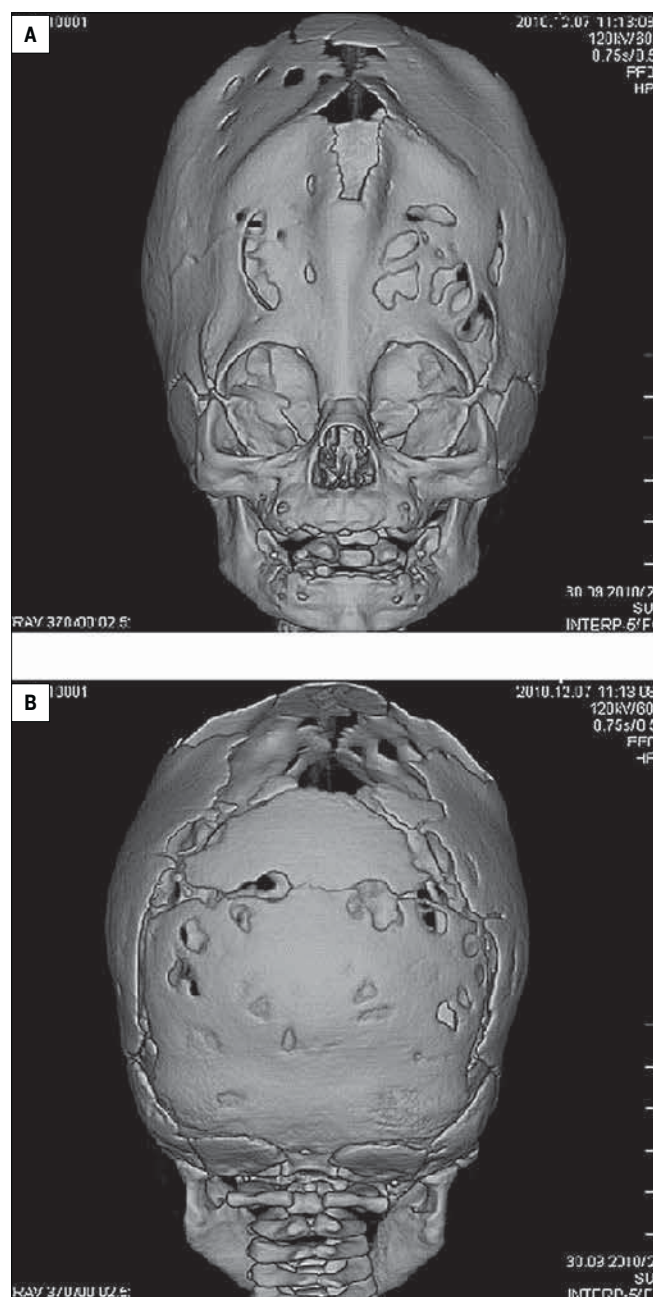


Figure 3. A three dimensional computed tomography scans of the 3-month-old boy with a multisutural craniosynostosis.

- A. Frontal view showing an ossification of the metopic suture on the level of the frontal bones and a large anterior fontanelle with a protruding additional bone in its projection.
B. Occipital view showing a partial ossification of the lambdoidal suture.

A prenatal diagnosis of a de novo *TWIST1* mutation has been reported only once and unlike in our case an abnormal cranial shape was only detected after birth. The genetic testing was performed due to a cardiac malformation, intrauterine growth retardation and facial dysmorphism [17].

In our patient no sonographically detectable extracranial abnormalities were observed. Prenatal karyotyping was performed because of the suspicion of craniosynostosis. The ultrasound visualization of the abnormal cranial shape was probably enabled by the fact that craniosynostosis included both the metopic and lambdoidal sutures (the coronal sutures were not ossified).

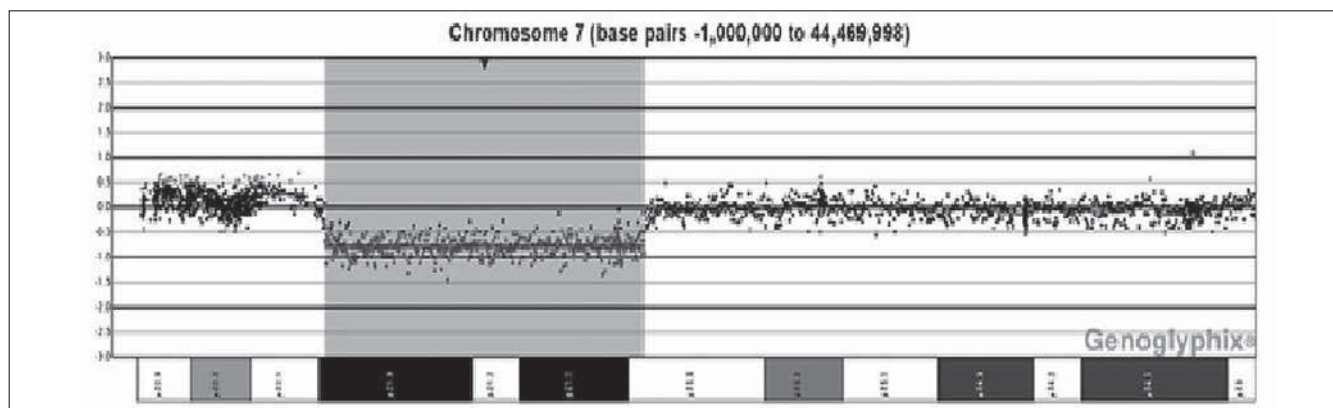


Figure 4. Array CGH. Schematic representation of the 7p21.3–7p15.3 microdeletion detected in our proband. The deleted region is shaded in grey. Data was visualized using Genoglyphix® Software (Signature Genomics).

A multisutural craniosynostosis is more typical for chromosomal rearrangements than classic SCS phenotype. However cases of SCS, caused by a 7p21–7p15 microdeletion, involving multiple cranial sutures have been reported [7].

In our case a precise genetic diagnosis was established only at the age of 2 years as the observed phenotype was primarily attributed to the apparently balanced de novo complex chromosomal rearrangement detected in prenatal karyotyping.

According to the literature phenotypic abnormalities are detected in around 6% of the cases of balanced complex chromosomal rearrangements and are probably caused by the disruption of the genes located at the breakpoints, additional micro-rearrangements at or close to the breakpoints (deletions, duplications or inversions), or position effects [18, 19]. A microdeletion 7p21.3–7p15.3, encompassing *TWIST1* gene, detected in the reported patient with an apparently balanced chromosomal rearrangement, is supposed to cause an observed compound SCS phenotype. To our knowledge, a case of craniosynostosis caused by a de novo complex chromosomal translocation with a microdeletion including *TWIST1* gene, has been previously reported only once [8].

Oświadczenie autorów

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