

CASE REPORT

Diagnostic and clinical approach to a paediatric patient with skin aplasia of the head as a rare manifestation of Xia-Gibbs syndrome caused by a new, potentially pathogenic *de novo* mutation in the *AHDC1* gene

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ABSTRACT

Xia-Gibbs syndrome is caused by pathogenic variants in the *AHDC1* gene. The characteristic features of the syndrome include delayed psychomotor and speech development, short stature, hypotonia, intellectual disability, structural brain anomalies, and mild facial dysmorphism. A boy came to the Genetic Outpatient Clinic due to skin aplasia of the head, facial dysmorphic changes, syndactyly of the second and third toes, delayed motor development, squamous haemangiomas on the head and face, hypoplasia of tooth enamel, excessively developed subcutaneous tissue, hypotonia, and joint laxity. In next-generation whole-exome sequencing a potentially pathogenic variant c.1913G>A, p.Trp638Ter was detected in a single allele of the *AHDC1*, resulting in premature termination of the protein. The boy's parents were not carriers of the lesion. Aplasia of the head's skin is an extremely rare discovery in the phenotype of patients with Xia-Gibbs syndrome. Next-generation sequencing allowed for an accurate diagnosis and detection of a mutation in the *AHDC1* gene.

KEY WORDS:

whole-exome sequencing, Xia-Gibbs syndrome, *AHDC1* gene.

INTRODUCTION

Xia-Gibbs syndrome (XIGIS, OMIM #615829) is a very rare disease with an incidence of < 1/1,000,000 births [1, 2]. The syndrome was described in 2014 for the first time by Xia *et al.*, who presented cases of 4 patients with this genetic disorder [3]. The cause is heterozygous mutations in the *AHDC1* gene located on the short arm of chromosome 1 (1p36.11-p35.3), which encodes a DNA-binding protein (AT-hook, DNA-binding motif-containing 1) [1, 3]. Xia-Gibbs syndrome is also known as *AHDC1*-related intellectual disability-obstructive sleep apnoea-mild dysmorphism syndrome. Ritter *et al.* reported a girl with Xia-Gibbs syndrome features with a chromosome microdeletion at 1p36.1-p35.3, which

included the *AHDC1* gene [4]. More than 270 individuals have been diagnosed worldwide so far [5, 6]. Xia-Gibbs syndrome is usually caused by a *de novo* pathogenic variant in the *AHDC1* gene [7]. The syndrome is characterised by the following features: hypotonia, absent or significantly delayed speech development, delayed psychomotor development, intellectual disability, obstructive sleep apnoea, sleep disorders, ataxia, mild facial dysmorphic features, structural brain anomalies, strabismus, seizures, short stature, autism spectrum disorder, scoliosis, laryngeal laxity, tracheomalacia, joint laxity, osteoarticular anomalies (for example clubfoot), movement disorders (ataxia, tremors, bradykinesia) occurring in childhood or teenage years, behavioural disturbances, epilepsy, ocular anomalies, nystagmus, cupped optic discs with unilateral

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FIGURE 1. Photograph of the head of the patient with Xia-Gibbs syndrome – occipital view. Note a characteristic feature: skin aplasia of the head

central macular dystrophy, craniosynostosis, bitemporal hollowing, brachycephaly, plagiocephaly, sucking and swallowing disorders, frequent vomiting, gastroesophageal reflux, and omphalocele [1, 2, 8–11]. Among structural brain anomalies, hypoplasia of the corpus callosum, simplified gyral pattern, delayed myelination, hypomyelination, cystic encephalomalacia, frontal and temporal cortical atrophy with loss of posterior ventricular white matter, subependymal or retrocerebellar cysts, cerebral atrophy, ventriculomegaly, and a small pituitary have been described [1, 3, 4, 8–10]. Facial dysmorphism includes concave nasal bridge, protuberant eyes, hairy, high, prominent forehead with prominent glabella, midface hypoplasia, strabismus, almond-shaped eyes, epicanthic fold, hypertelorism, up- or down-slanting palpebral fissures, flat nasal bridge, thin upper lip, highly arched palate, tented upper lip, prominent teeth, low-set or protuberant ears, and micrognathia [1, 8–10]. The aim of this study is to present the medical history of a patient with skin aplasia of the head as a rare manifestation of Xia-Gibbs syndrome, paying attention to the diagnostic process.

CASE REPORT

The patient was referred to the Genetic Outpatient Clinic at the age of 9 months for diagnosis due to skin aplasia of the head, facial dysmorphic features, syndactyly of the second and third toes, and delayed motor development. Both parents were healthy, nonconsanguineous Caucasians. At the moment of delivery, the mother was 26 years old and the father – 28. The father worked in a furniture factory. The patient had no siblings. During



FIGURE 2. Photograph of the face of the patient with Xia-Gibbs syndrome – front view. Note characteristic features: long philtrum, concave nasal bridge

her pregnancy, the mother experienced vaginal inflammation and infections. From the 28th week of pregnancy, the uterine cervix was shortening. The results of each ultrasound examination were normal. During pregnancy, the mother took vitamins and lutein. The boy was born from the first pregnancy, first delivery, at 39 weeks of pregnancy by caesarean section with a body weight of 3970 g. He received 10 points on the Apgar scale. Birth length of the body was 58 cm, head circumference 35 cm, and chest circumference 36 cm. Physical examination of the patient revealed aplasia of the scalp in the occiput area in the midline of the body (according to medical documentation and parents' claim: from the neonatal period) (Figure 1). In a computed tomography of the head the bone structures of the skull did not show any pathological changes. The proband exhibited other features as follows: scars on the scalp after skin defects, squamous haemangiomas on the head and face, atopic, delicate skin, numerous pimples on the skin of the scrotum, hypoplasia of tooth enamel, excessively developed subcutaneous tissue, concave nasal bridge, long philtrum, delicate unilateral epicanthic fold, deep-set eyeballs, strabismus, syndactyly of the second and third toes, delicate umbilical hernia, small penis, wandering testicles, hypotonia, and joint laxity (Figures 1–5). Psychomotor development was delayed. At the age of 10 months, the patient sat unsteadily, pronounced syllables, and muscle hypotonia was observed. At the age of 14 months, the patient did not sit on his own, but sat when seated. He could say 2 words and would stand when an adult held his hands. He was rehabilitated. Electroencephalogram examination was normal. At the age of 20 months, the patient sat and stood up independently, walked by hand, could speak 2 words, was cheerful, and played with toys. At the age of 3 years the boy could speak 6 words, understood a lot, was calm,



FIGURE 3. Photograph of the head of the patient with Xia-Gibbs syndrome – side view. Note a characteristic feature: slightly elongated skull



FIGURE 4. Photograph of hands of the patient with Xia-Gibbs syndrome. Note a characteristic feature: puffy hands



FIGURE 5. Photograph of the feet of the patient with Xia-Gibbs syndrome. Note a characteristic feature: syndactyly of the second and third toes of both feet

polite, and observed the surroundings. At the age of 4 he spoke about 10 words and understood everything. He attended a special kindergarten and rehabilitation classes. The patient wore glasses due to strabismus. At the age of 4.5 years the boy speaks about 15 words and likes reading books. According to his parents, he drools a lot, eats everything with an appetite, but has problems with biting. Rehabilitation improved the patient's balance.

Genetic diagnosis started with excluding Gorlin-Goltz syndrome. Sanger sequencing of exons 1–14 of the *PORCN* gene was performed. No mutations were detected. Next-generation whole exome sequencing (NGS WES) was ordered. A new, potentially pathogenic variant c.1913G>A, p.Trp638Ter was detected in a single allele of the *AHDC1* gene on chromosome 1, resulting in premature termination of the protein (NM_001029882.2:c.1913G>A, NP_001025053.1:p.Trp638Ter, Chr1:27876714C>T). The correlation of genetic test results with the patient's phenotypic characteristics indicated Xia-Gibbs syndrome. His parents were not carriers of that lesion.

DISCUSSION

The *AHDC1* gene encodes a protein containing 2 AT-hooks with a potential function in DNA binding, process of transcription, and epigenetic regulation [12]. The function of the gene is not fully understood. The pathogenic variant p.Trp638Ter in a single allele of the *AHDC1* gene on chromosome 1 results in premature termination of the protein. That is why it may explain the interaction with brain function and neurodevelopment leading to the phenotypic features mentioned in the case report.

As far as clinical features in our patient are concerned, it is crucial to collate them with clinical features of other patients diagnosed with Xia-Gibbs syndrome. Romano *et al.* set together the main clinical features in Xia-Gibbs patients described in the literature as well as 5 more patients investigated by him, dividing these features into “cardinal” core signs and other minor clinical manifestations [3, 4, 6, 8–10, 12–16]. Common features include intellectual disability, speech delay, motor delay, hearing deficit, structural brain abnormality, ataxia, sleep apnoea, autism, hypotonia at diagnosis, seizures, scoliosis, strabismus, and short stature. Laryngomalacia, tracheomalacia, osteoarticular anomalies, hypothyroidism, and aplasia cutis were listed as uncommon, rare features. The clinical features of our patient are compared with other patients in Table 1 [3, 4, 6, 8–10, 13–16].

It can be clearly seen from the table that our patient manifested some clinical features that were common among almost all patients portrayed in the table such as intellectual disability, speech delay, motor delay, and hypotonia. However, our patient clearly depicts some other features that were not present in other patients, although many of them were reported in literature that was

TABLE 1. Main clinical features in Xia-Gibbs patients including our case

Clinical feature	Xia <i>et al.</i> [3]	Yang <i>et al.</i> [10]	Bosch <i>et al.</i> [13]	Garcia- Acero <i>et al.</i> [8]	Jiang <i>et al.</i> [14]	Ritter <i>et al.</i> [4]	Gumus [9]	Cardoso-Dos Santos <i>et al.</i> [15]	Khayat <i>et al.</i> [6]	Ellis <i>et al.</i> [16]	Total	Our case
Intellectual disability	4/4	7/8	NA	+	NA	4/5	+	+	30/34	+	49/76	+
Speech delay	4/4	7/8	+	+	NA	5/5	+	+	32/34	+	53/76	+
Motor delay	4/4	6/8	+	+	NA	5/5	+	+	32/34	+	52/76	+
Hearing deficit	NA	NA	NA	NA	NA	1/5	NA	NA	NA	+	2/76	–
Structural brain abnormality	4/4	6/8	NA	+	12/20	3/5	+	NA	NA	–	27/76	–
Ataxia	NA	NA	NA	NA	13/20	NA	NA	+	23/34	–	37/76	–
Sleep apnoea	3/4	2/8	+	+	9/20	3/5	NA	+	17/34	+	38/76	–
Autism	NA	NA	NA	NA	5/20	NA	NA	NA	10/34	+	16/76	–
Hypotonia at diagnosis	4/4	NA	NA	NA	18/20	4/5	+	NA	30/34	+	58/76	+
Seizures	NA	NA	NA	NA	6/20	NA	+	+	15/34	+	24/76	–
Scoliosis	–	1/8	NA	–	4/20	–	–	+	9/34	–	15/76	–
Strabismus	–	3/8	NA	–	8/20	–	+	–	14/34	–	26/76	+
Short stature	–	2/8	NA	–	NA	NA	–	–	17/34	–	19/76	–
Laryngomalacia	2/4	–	NA	+	–	–	–	–	6/34	+	10/76	–
Tracheomalacia	1/4	NA	NA	–	NA	–	–	–	3/34	–	4/76	–
Osteo-articular anomalies	–	3/8	NA	–	–	4/5	–	–	1/10	+	9/76	–
Hypothyroidism	–	–	NA	–	–	–	–	–	–	–	0/76	–
Aplasia cutis	–	–	NA	–	–	1/5	–	–		+	2/76	+
Facial dysmorphic features	4/4	6/8	+	+	7/20	2/5	+	+	10/10	+	34/76	+
Syndactyly of the 2 nd and 3 rd toes	–	NA	NA	NA	NA	1/5	–	NA	NA	NA	1/76	+
Squamous haemangiomas on the head and face	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/76	+
Numerous pimples on the skin of the scrotum	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/76	+
Hypoplasia of tooth enamel	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/76	+
Excessively developed subcutaneous tissue	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/76	+
Concave nasal bridge	3/4	NA	NA	NA	7/20	1/5	NA	NA	1/10	+	13/76	+
Long philtrum	NA	NA	NA	NA	NA	–	NA	NA	NA	–	0/76	+
Delicate unilateral epicanthic fold	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	1/76	+
Deep-set eyeballs	NA	NA	NA	NA	4/20	–	NA	NA	NA	+	5/76	+
Delicate umbilical hernia	NA	NA	NA	NA	NA	–	NA	NA	NA	NA	0/76	+

TABLE 1. Cont.

Clinical feature	Xia <i>et al.</i> [3]	Yang <i>et al.</i> [10]	Bosch <i>et al.</i> [13]	Garcia- Acero <i>et al.</i> [8]	Jiang <i>et al.</i> [14]	Ritter <i>et al.</i> [4]	Gumus [9]	Cardoso-Dos Santos <i>et al.</i> [15]	Khayat <i>et al.</i> [6]	Ellis <i>et al.</i> [16]	Total	Our case
Small penis	NA	NA	NA	–	NA	–	NA	NA	NA	NA	0/76	+
Atopic, delicate skin	NA	NA	NA	–	NA	1/5	NA	NA	NA	NA	1/76	+
Wandering testicles	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	0/76	+
Joint laxity	NA	2/8	NA	–	NA	4/5	NA	NA	NA	NA	6/76	+

NA – not available

mentioned in the introduction part of this study. Based on the literature, there is still a lack of the specific genotype-phenotype correlation in Xia-Gibbs syndrome, and further investigation on future newly reported patients must be done to identify more specific dependence.

Ellis *et al.* described a patient who presented with aplasia of the skin in association with Xia-Gibbs syndrome. The girl presented with several small ulcerations on the scalp with surrounding hypotrichosis and thinning of the parietal bone and skin in magnetic resonance imaging. The lesions healed with alopecia and remnant scarring [16]. Ritter *et al.* presented a patient with cutis aplasia of the scalp noted at birth [4]. To our best knowledge, our patient is the third case with Xia-Gibbs syndrome and skin aplasia of the head. It is worth underlining that aplasia of the skin of the head may not only be a symptom of Xia-Gibbs syndrome but could arise because of intrauterine factors during pregnancy. Many authors claim the effect of amniotic fluid quantity disorders, vascular anomalies, embolisms, external injuries, intrauterine infections, viruses, or pharmacological teratogenic substances [17–25]. Vaginal inflammation and infections of the mother of our patient could contribute to the occurrence of the above-mentioned symptoms.

Differential diagnosis of Xia-Gibbs syndrome should include other genetic syndromes with aplasia cutis; for example, some types of Adams-Oliver syndrome. Adams-Oliver syndrome is a rare inherited disorder identified by congenital scalp defects and terminal limb abnormalities, with severity varying among individuals [26]. Some of the cases share similar phenotype characteristics to Xia-Gibbs syndrome such as structural and central nervous system anomalies [27]. Skin aplasia of the scalp is also described in some other disorders, like Patau, Wolf-Hirschhorn, Johanson-Blizzard, or Finlay-Marks syndromes [28]. It is crucial to bear in mind the aspect of similar phenotype syndromes, especially the aplasia cutis, which is present in those disorders.

Variants of *AHDC1* are associated with an ectoderm disease phenotype. Its expression similarly echoes the expression of mesoderm genes, resulting in their regulation during early embryonic development. The protein Gibbin, encoded by the *AHDC1* gene, is a key regulator of epithe-

lial morphogenesis. Mesodermal DNA methylation and DNA methyltransferase regulation are vulnerable to Gibbin output. Gibbin loss may increase in DNA methylation depending on GATA3 (transcription factor) mesodermal genes. This may result in a disturbance in signalling between developing dermal and epidermal cell types. Mutation in *AHDC1* can eventually cause a lack of dermal maturation. It is indicated that clinical features seen in Xia-Gibbs syndrome, like intellectual disability, craniofacial defects, or ectodermal dysplasia, might derive from abnormal mesoderm maturation as a result of gene-specific DNA methylation decisions [29].

The natural course of the disease is not fully known. Only a few cases of adults with Xia-Gibbs syndrome have been documented in the literature [30]. Previous studies have found growth hormone replacement therapy and physical therapy intervention to be effective. As far as life expectancy is concerned, it is still not possible to assess this factor because the number of reported adult patients is very modest. Few reported patients were between 30 and 40 years old, and the oldest patient was a 55-year-old male [30].

Age-appropriate cancer screening is recommended for patients with Xia-Gibbs syndrome [30]. The same applies to the issue of hypertension because of the increased vulnerability of the discussed patients [30].

CONCLUSIONS

Patients with Xia-Gibbs syndrome can have a broad clinical spectrum of symptoms. Aplasia of the head's skin is an extremely rare discovery in the phenotype of patients with Xia-Gibbs syndrome. The cause of the patient's phenotypic features was found due to appropriate genetic testing. Next-generation sequencing allowed for an accurate diagnosis and detection of a previously unknown mutation in the *AHDC1* gene leading to Xia-Gibbs syndrome.

DISCLOSURES

1. This study was approved by the Ethics Committee of the Medical University of Lublin, Poland (committee reference number: KE-0254/228/11/2022). Consent of the Head of the University Children's Hospital in Lu-

blin for access to patients' medical documentation was obtained (No. 13/BN/2023 of 23 May 2023).

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4. Conflicts of interest: None.

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