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Case Report

Phenotypic variability in children with Bruck syndrome type 2: Clinical cases

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ABSTRACT

BACKGROUND: Bruck syndrome is a rare disorder that features osteogenesis imperfecta, combined with severe congenital joint contractures often with pterygia, short stature, severe limb deformities, and progressive scoliosis. Its two forms, Bruck syndrome types 1 and 2, have similar clinical manifestations without osomal recessive inheritance and are caused by pathogenic variants of the nucleotide sequences in the *FKBP10* and *PLOD2* genes, respectively.

CLINICAL CASES: The article demonstrates phenotypic and radiographic features as well as laboratory values of siblings with Bruck syndrome type 2 (a 10-year-old boy and a 13-year-old girl) born to healthy parents in a consanguineous marriage. The boy had congenital flexion contractures of the knee and elbow joints, few fractures, and severe kyphoscoliosis. The girl had no congenital joint contractures but had kyphoscoliosis, more severe osteoporosis, and a history of having more fractures than her younger brother.

DISCUSSION: The cases demonstrated the significant phenotypic intrafamilial variability of Bruck syndrome type 2, caused by a newly identified homozygous variant c.1885A>G (p.Thr629Ala) in *PLOD2*, which consists of varying degrees of osteoporosis, and the presence and severity of contractures.

CONCLUSIONS: The description of the given clinical observation was made to draw attention to a rare pathology and expand doctors' knowledge about the variability of clinical manifestations of Bruck syndrome. Genetic diagnostics is necessary for the timely diagnosis of Bruck syndrome, determining the prognosis and developing patient management techniques.

Keywords: Bruck syndrome; osteogenesis imperfecta; arthrogryposis; collagen; contractures; osteoporosis; fractures; kyphoscoliosis; *FKBP10* gene; *PLOD2* gene.

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Клинический случай

Фенотипическая вариабельность у детей с синдромом Брука 2-го типа: клинические наблюдения

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АННОТАЦИЯ

Обоснование. Синдром Брука представляет собой редкое заболевание, при котором симптомы несовершенного остеогенеза сочетаются с тяжелыми врожденными контрактурами суставов, кожными птеригиумами, низким ростом, тяжелыми деформациями конечностей и прогрессирующим сколиозом. Две его формы, синдром Брука 1-го и 2-го типов, схожи по клиническим проявлениям, наследуются аутосомно-рецессивно и обусловлены патогенными вариантами нуклеотидной последовательности в генах *FKBP10* и *PLOD2* соответственно.

Клинические наблюдения. В статье демонстрируются фенотипические и рентгенографические признаки, а также лабораторные показатели родных брата и сестры с синдромом Брука 2-го типа: мальчика 10 лет и девочки 13 лет, рожденных от здоровых родителей в близкородственном браке. У мальчика наблюдались врожденные сгибательные контрактуры коленных и локтевых суставов, небольшое количество переломов, в течение жизни сформировался тяжелый кифосколиоз. У девочки врожденных контрактур суставов не было, отмечались кифосколиоз, более выраженный остеопороз и большее количество переломов в анамнезе по сравнению с младшим братом.

Обсуждение. Представленные нами случаи показывают значительную фенотипическую внутрисемейную вариабельность синдрома Брука 2-го типа, обусловленного вновь выявленным гомозиготным вариантом c.1885A>G (p.Thr629Ala) в гене *PLOD2*, — различную степень остеопороза, а также наличие и выраженность контрактур.

Заключение. Клинические наблюдения рассмотрены с целью привлечения внимания к редкой патологии и расширения знаний врачей об изменчивости клинических проявлений синдрома Брука. Для своевременной диагностики синдрома Брука и определения прогноза развития заболевания, а также выработки обоснованной тактики лечения пациента необходимо проведение молекулярно-генетического исследования.

Ключевые слова: синдром Брука; несовершенный остеогенез; артрогрипоз; коллаген; контрактуры; остеопороз; переломы; кифосколиоз; ген *FKBP10*; ген *PLOD2*.

Как цитировать
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BACKGROUND

Bruck syndrome is a rare disease that presents with combined symptoms of osteogenesis imperfecta and severe congenital joint contractures similar to those in arthrogryposis [1–3]. Osteogenesis imperfecta is a genetically heterogeneous disease caused by impaired type I collagen synthesis. It is characterized by frequent fractures, blue sclera, and in some cases, hearing loss [2]. Patients with Bruck syndrome present with severe bilateral joint contractures, cutaneous pterygiums, short stature, severe limb deformities, progressive scoliosis, and brittle bones.

Bruck syndrome is a combination of two rare autosomal recessive diseases that have similar clinical presentations but are caused by pathogenic nucleotide sequence variants in two different genes. Bruck syndrome type 1 is caused by biallelic variants in the FKBP10 gene (OMIM#607063), which is responsible for the synthesis of FK506-binding protein 10. This protein interacts with lysyl hydroxylase-2 (LH2) and regulates its activity. Bruck syndrome type 2 is associated with biallelic variants in the PLOD2 gene (OMIM#601865), which is crucial in LH2 synthesis. Insufficient lysine hydroxylation in the telopeptide of collagen occurs because of bone-specific telopeptide lysylhydroxylase-2 deficiency, leading to a decrease in hydroxylysylpyridinoline cross-links and improper cross-linking of bone collagen [4–6].

Phenotypic differences between Bruck syndrome types 1 and 2 have not been previously described [7, 8]. Here, we present clinical cases of Bruck syndrome type 2 in siblings (a brother and sister) with significant differences in clinical manifestations.

CLINICAL OBSERVATIONS

The children's father and maternal grandfather are cousins. Of the three children in the family, the eldest is healthy, whereas the two younger ones, a boy and a girl, have been diagnosed with Bruck syndrome type 2. Currently, the mother is pregnant with the fourth child. The parents of the children are healthy. The diagnosis was confirmed by sequencing a targeting panel of 166 genes responsible for hereditary skeletal pathology development. Analysis was conducted using the Ion Torrent S5 sequencer with an average coverage of at least 80 and target regions with at least 20 ⩾90%–94% coverage. The standard automated algorithm offered by Ion Torrent was used for primary sequencing data processing. Genomic DNA was isolated from whole blood using the DNAEasy kit (QiaGen, Germany) following the manufacturer's standard protocol. DNA and DNA library concentrations were measured on a Qubit2.0 instrument using reagents (Qubit BR, Qubit HS) following the manufacturer's standard protocol. For sample preparation, a technique based on the multiplex polymerase chain reaction of targeted DNA sections was used. Population frequencies of the detected variants were estimated using samples from the 1000 Genomes project, ESP6500, and The Genome Aggregation Database v2.1.1. The clinical relevance of the detected variants was determined using the OMIM database and HGMD® Professional Pathogenic Variants Database, version 2022.1. Pathogenicity and the cause of genetic variants were analyzed according to international recommendations for interpreting data obtained using mass parallel sequencing methods [9]. Variants identified in the older child were confirmed by direct automatic Sanger sequencing using an ABIPrism 3100 instrument (Applied Biosystems) according to the manufacturer's protocol. Genotyping of his parents and younger sister was performed using the same method. The primer sequences were selected based on the reference sequence of *PLOD2* target sites (NM_182943.3).

In one of the siblings (boy), a previously described pathogenic variant was found in the homozygous state. The variant affects the nucleotide sequence in exon 18 of the *PLOD2* gene (OMIM#601865) and results in the substitution of threonine amino acid for alanine (p. Thr629Ala). In the other sibling (girl), the same variant in the *PLOD2* gene in the homozygous state as in her brother was found through Sanger direct automatic sequencing. Both their parents were heterozygous carriers of the detected variant in the *PLOD2* gene. Prenatal diagnosis of the fetus allowed for the detection of the same variant in the heterozygous state, which was the cause of the postterm pregnancy.

Clinical case 1

Patient H, delivered independently during the second term of her mother's second pregnancy, had a birth weight of 3900 g and a height of 52 cm. No orthopedic pathology was detected. Since birth, patient H has been under the supervision of a neurologist because of birth trauma to the central nervous system. At age 1, patient H stopped standing and making attempts to walk. At age 3, the patient experienced a left femur fracture for the first time. Compression fractures of the Th_{XII}–L_I vertebrae were detected when she was 4 years old. She suffered three fractures of the right and left femur between the ages of six and eight. At age 6, examination showed a decrease in skeletal bone mineral density. Bisphosphonates were administered twice a year to treat osteoporosis, which helped reduce fractures. At age 8, corrective osteotomy of the right and left femur was performed for the first time, with fixation using a telescopic rod (Fig. 1). Standard consolidation periods followed osteotomy.

Currently, patient H is a 13-year-old girl with a hypersthenic body build and a height of 125 cm. She uses crutches to walk indoors. Her head is positioned along the midline, and her neck is short. Mandibular asymmetry with displacement

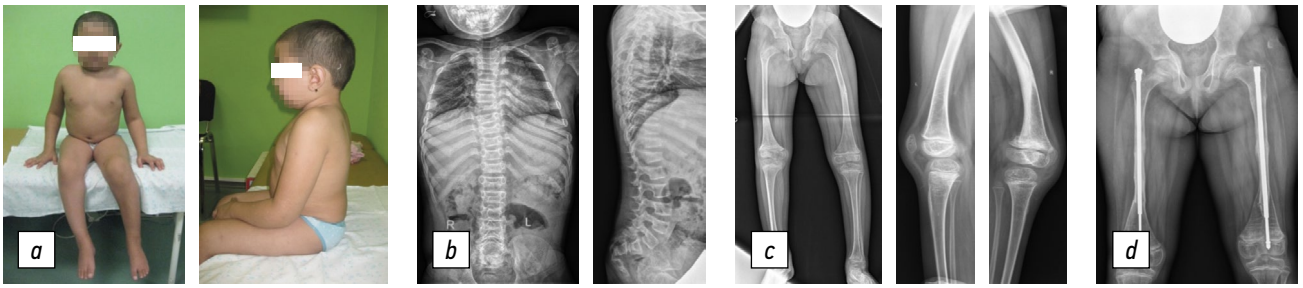

Fig. 1. Patient H, eight years old, Bruck syndrome, type 2: *a*, general view of the patient (does not walk); *b*, spine radiographs in anteroposterior and lateral projections: 10° frontal deviation of the spinal axis, wedge-shaped vertebrae; *c*, panoramic radiograph of the lower extremities in anteroposterior projection, varus-antecurvation deformity of the femurs; *d*, radiograph of the femurs in anteroposterior projection, intramedullary fixation with a telescopic rod

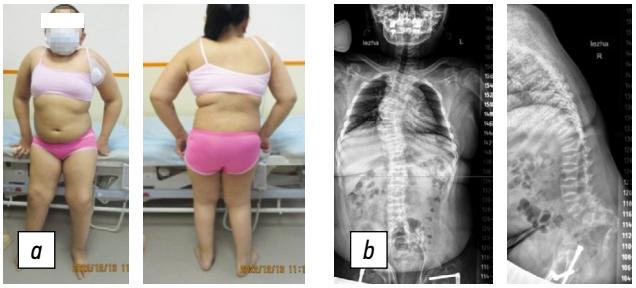

Fig. 2. Patient H, 13 years old, Bruck syndrome, type 2: *a*, general view of the patient; *b*, anteroposterior and lateral radiographs of the spine: 40° right scoliotic deformity, 33° kyphosis, platyspondylia, and sacrococcygeal changes

to the right is noted. The spinal axis is curved in both the frontal and sagittal planes, resulting in kyphoscoliosis in the thoracolumbar region and hyperlordosis in the lumbar region. No limitations are observed in the movements of the shoulder, elbow, and wrist joints, and the hands are in a neutral position. Additionally, a valgus deformity is present in the right lower extremity. There is flexion in the hip joints up to 90°, with minimal rotational movements that are moderately painful. There is a 20° extension deficit in the knee joints, and flexion is possible up to 80° on both sides. The feet are in a neutral position.

The anteroposterior and lateral projections of the panoramic radiograph of the spine revealed a kyphotic deformity of 33° (Th_{IX}–L_{II}) and a scoliotic deformity of 40° (Th_{IX}–L_{XII}), with the sacrum horizontal and coccyx at a 90° angle (Fig. 2). Magnetic resonance imaging of the craniovertebral region indicated an Arnold-Chiari anomaly of the first degree. Table 1 presents the densitometry parameters' dynamics between the ages of 6 and 13 years. After a long period of gradual increase, a repeated decrease in skeletal bone mineral density due to a long treatment break (9.5–11 years) was observed. Blood analysis showed high C-terminal telopeptide (2.63 ng/mL; normal range: 1.63–1.94 ng/mL) at the beginning of treatment. Currently, the level has normalized (1.68 ng/mL). Throughout the observation period, persistent and pronounced vitamin D deficiency (last value: 7.3 ng/mL; normal range: 30–80 ng/mL) was detected. The additional parameters of bone tissue metabolism, including calcium, phosphorus, alkaline phosphatase, osteocalcin, N-terminal propeptide, and parathormone, were within normal limits.

Table 1. Dynamics of densitometry parameters of patient H

Age, years	Skeleton			L_I–L_{IV}		
	BMD, g/cm²	Z-criterion	%	BMD, g/cm²	Z-criterion	%
6	0.484	–3.2	74	0.381	–3.6	59
6.5	0.502	–2.8	76	0.394	–3.4	60
7	0.519	–2.6	78	0.463	–2.5	70
7.5	0.577	–1.7	84	0.537	–1.6	80
8	0.594	–1.6	85	0.590	–1.1	87
9	0.635	–1.2	88	0.639	–0.7	91
9.5	0.641	–1.4	86	0.619	–1.2	84
11	0.661	–1.7	83	0.616	–1.9	75
12	0.686	–1.9	81	0.588	–2.8	65
12.5	0.714	–1.8	82	0.777	–1.5	81
13	0.695	–2.2	79	0.797	–1.4	83

Note: BMD, bone mineral density.

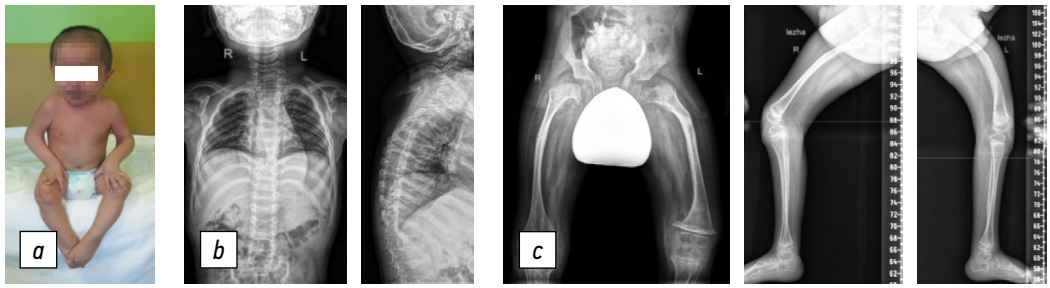

Fig. 3. Patient I, 4 years old, Bruck syndrome, type 2: *a*, general view of the patient; *b*, spine radiographs in anteroposterior and lateral projections: 45° kyphosis, decreased height, and wedge-shaped vertebrae; *c*, panoramic radiographs of the lower extremities in anteroposterior and lateral projections: varus-antecurvation deformity of the femur bones

Clinical case 2

Patient I, delivered independently during the third term of his mother's third pregnancy, had a birth weight of 2700 g and a height of 51 cm. At birth, patient I had flexion contractures of the elbow and knee joints at a 90° angle, ulnar and hamstring skin pterygium, equino-valgus deformities of the feet, skin pulling in the knee joint area, protruding frontal tubercles, and plagiocephaly. At age 1, he underwent stage plastering of the feet, achillotomy, and orthotization. At age 2, the patient underwent posterior medial release on both the right and left feet. Simultaneously, stage plastering was performed to eliminate flexion contractures of the elbow joints. Before treatment, the extensor deficit was 60° on both sides. Following treatment, it decreased to 30°. At age 3, to eliminate flexion contractures of the knee joints, lengthening of the tibial flexors on both sides was performed, followed by correction with plaster casts. The knee joint extensibility deficit before surgery was 70°; however, it completely improved after treatment. The child experienced recurrent flexion contractures in the elbow and knee joints during growth, which required repeated correction with staged plastering and subsequent orthotization. After the elimination of knee joint contractures, the boy was able to walk with assistance within the house. However, he lost this ability after relapse. At age 3, he experienced a fracture in the upper third of his left femur for the first time. Examination revealed a decrease in bone mineral density (Fig. 3). Bisphosphonates were administered parenterally twice a year from age four to the present to treat osteoporosis, resulting in a decrease in fractures. At age 5, corrective osteotomy of the right and left femur at two levels was performed to correct femoral bone deformity, followed by fixation with a telescopic rod. Standard consolidation periods were observed.

The boy is currently 10 years old and can sit independently but cannot walk. He has a height of 116 cm and a brachycephalic head. His face is symmetrical with protruding frontal tubercles, and his neck is short. The spinal axis is curved in the sagittal plane. Specifically, the cervical region is straight; local kyphosis in the thoracolumbar transition area and hyperlordosis in the lumbar region are noted. Additionally, a left-sided scoliotic deformity is determined in the thoracolumbar region. The length of the upper limbs is equal, and there are no limitations in the movements of the shoulder joints. There is a 40° flexion deficit in the right elbow joint and a 50° flexion deficit in the left elbow joint. Hand function is not impaired. The left lower limb is relatively short by 2.5 cm. Flexion contractures of the hip joints with a deficit of extension of 40° and flexion up to 60° on both sides were noted, as well as flexion contractures of the knee joints with a deficit of extension of 50° and flexion up to 80° on both sides. Additionally, an equinovalgus deformity of both feet was observed.

Radiographs of the spine in frontal and lateral projections revealed local pathologic kyphosis in the thoracic region

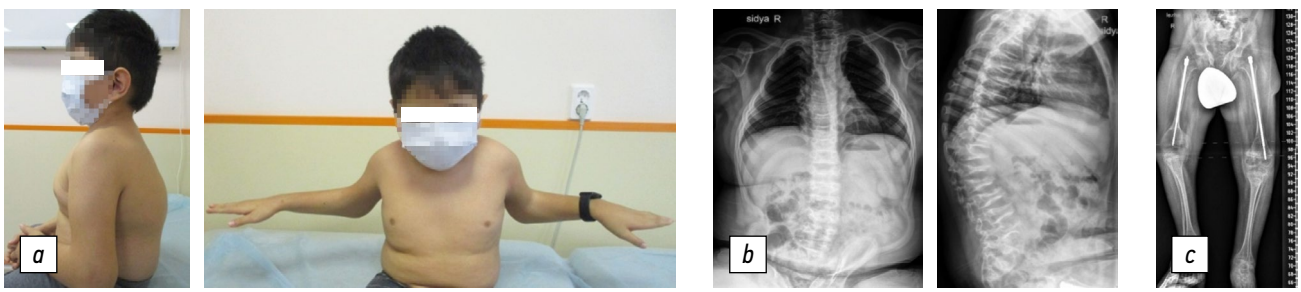

Fig. 4. Patient I, 10 years old, Bruck syndrome type 2: *a*, general view of the patient; *b*, anteroposterior and lateral projection radiographs of the spine: local pathologic kyphosis in the thoracic region, 45° with decreased height and wedge-shaped vertebral bodies, hyperlordosis in the lumbar region, and 26° left-sided scoliotic arch in the thoracolumbar region; *c*, panoramic radiograph of the lower extremities in the anteroposterior projection: intramedullary fixation of the femurs with telescopic rods

Table 2. Dynamics of the densitometry parameters of patient I

Age, years	Skeleton			L_I–L_{IV}		
	BMD, g/cm²	Z-criterion	%	BMD, g/cm²	Z-criterion	%
4	0.471			0.229		
5	0.490	–3.0	79	0.294	–5.1	47
5.5	0.517	–2.5	81	0.390	–3.6	61
6	0.531	–2.3	84	0.441	–2.5	69
6.5	0.548	–2.2	84	0.455	–2.5	70
8	0.611	–1.5	88	0.519	–1.9	76
9	0.609	–2.0	84	0.435	–3.0	61
9.5	0.668	–1.3	89	0.643	–0.9	87
10	0.647	–1.7	85	0.684	–0.6	92

Note: BMD, bone mineral density.

of 45°, platyspondylia, wedge-shaped vertebral bodies, hyperlordosis in the lumbar region, and a left-sided scoliotic arch in the thoracolumbar region of 26° (Fig. 4). Table 2 presents the densitometry data. The observation period revealed pronounced vitamin D deficiency (level: 12 ng/mL; normal range: 30–80 ng/mL). Additionally, increased levels of C-terminal telopeptide (up to 2.6 ng/mL; normal: 1.63–1.94 ng/mL) and N-terminal propeptide (1037 ng/mL at the beginning of treatment; 649 ng/mL at present; normal: 388–571.6 ng/mL) persisted. However, all other indices of bone tissue metabolism, including calcium, phosphorus, alkaline phosphatase, osteocalcin, and parathormone, were within normal limits.

DISCUSSION

Since its description in 1897, multiple congenital joint contractures have been the main differential criterion used to distinguish Bruck syndrome from osteogenesis imperfecta [2, 10].

At 3 years old, the patient presented with symptoms resembling osteogenesis imperfecta, including osteoporosis, frequent fractures, and progressive scoliosis, but without contractures of major joints or cutaneous pterygiums. Atypical clinical presentation hindered accurate diagnosis by physicians at that time. The patient's younger brother had been treated for arthrogryposis since birth. Bruck syndrome was suspected only after the first fracture occurred. The presence of characteristic signs of the disease in the boy, such as congenital contractures and frequent fractures, indicated Bruck syndrome in his sister as soon as both children came to our attention. Molecular genetic analysis confirmed the diagnosis of Bruck syndrome type 2 with autosomal recessive type of inheritance, as a new variant c.1885A>G (p. Thr629Ala) in the *PLOD2* gene was found in the patients in homozygous state and in their healthy parents in heterozygous state.

Therefore, distinguishing between Bruck syndrome and osteogenesis imperfecta without genotyping is challenging when minimal joint contractures are present. To ensure an accurate diagnosis and assess the prognosis for each patient and their offspring, a genetic testing protocol for patients with osteoporosis should be included in diagnosing Bruck syndrome [1, 3, 11, 12].

The presented cases demonstrate the phenotypic intrafamilial variability of Bruck syndrome type 2, which includes varying degrees of osteoporosis and the presence and severity of contractures. Table 3 summarizes the phenotypic differences between siblings.

Bruck syndrome is a rare condition; hence, studies on the treatment principles for this disease are lacking. Currently, treatment is similar to that for osteogenesis imperfecta [2]. Treatment involves parenteral administration of bisphosphonates and surgical correction of limb bone deformities with intramedullary fixation. Both diseases have been effectively treated; however, Bruck syndrome has a poorer prognosis because of joint contractures [6]. Patients who experience frequent fractures may have limited mobility, and multiple joint contractures can further reduce their functional activity. Despite surgical correction of limb deformities, patient I is still unable to walk because of recurrence of flexion contractures of large joints. In contrast, patient H, who had worse densitometry and a history of more fractures, is able to move independently.

CONCLUSIONS

The clinical observation of patients with Bruck syndrome type 2, a rare disease, emphasizes the uniqueness of such conditions on orphan pathology. In the patients we described with a newly identified variant in the *PLOD2* gene, the disease had different phenotypic manifestations, which may complicate timely diagnosis and treatment. Molecular genetic studies are useful in cases of

Table 3. Phenotypic differences between siblings with Bruck syndrome type 2

Signs	Patient I (brother)		Patient H (sister)	
	Description	Age of onset/ development	Description	Age of onset/ development
Contractures	Flexion contractures of the elbow and knee joints, equinus contracture of the ankle joints on both sides	Temporary improvement at birth/after surgical and conservative treatment, followed by relapse	Upper and lower limbs without contractures	–
Spinal deformity	Local pathologic 45° kyphosis in the thoracic spine, platyspondylia	By age nine/corset	Local 33° kyphosis (Th_{IX}–L_{II}), 40° scoliosis (Th_{X}–Th_{XII}), platyspondylia, sacral spinal anomaly, Arnold-Chiari anomaly	By age 13/ conservative treatment (physical therapy, massage)
Fractures	Three fractures of the right and left femurs, compression fractures of the thoracic and lumbar vertebrae	By age three and five	Six fractures: right and left femurs, Th_{XII}–L_{I} compression fractures	By age three, four, seven, and eight
Ability to move	Can stand, cannot walk	By age three/worsening after fractures and recurrence of contractures	Can walk	By age one/ worsening after fractures
Height	Low (<1st percentile)	By age 10 Height: 116 cm	Low (<1st percentile)	By age 13 Height: 125 cm
Craniofacial anomalies	Plagiocephaly, protruding frontal tubercles	From birth	Asymmetry of the mandible, displacement to the right	From birth
Densitometry data (latest study)	Skeleton: BMD, 0.714, Z-criterion, 1.8; L_{I}–L_{IV}: BMD, 0.770, Z-criterion, 1.5	By age 10	Skeleton: BMD, 0.659, Z-criterion, 2.2; L_{I}–L_{IV} BMD, 0.797, Z-criterion, 1.4	By age 13

minimally expressed joint contractures to differentiate Bruck syndrome from other similar diseases based on clinical manifestations. This helps determine the prognosis and appropriate management tactics for patients and their families and provides effective medical and genetic counseling.

ADDITIONAL INFORMATION

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Ethical review. Informed consent was obtained from the patients' representatives for molecular genetic testing of blood samples and publication of personal data.

Authors' contribution. *S.I. Trofimova*, concept development, text editing, surgical treatment of patients; *E.A. Kochenova*, data collection, preparation of the text of the article, conservative treatment of patients; *O.E. Agranovich*, text editing, approval of the final version of the article; *D.S. Buklaev*, text editing, surgical treatment of patients; *E.S. Merkuryeva*, *T.V. Markova*, medical and genetic counseling and examination of patients, text editing of the article.

All authors made significant contributions to the study and article preparation and read and approved the final version before publication.

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