SURGICAL TREATMENT OF A PATIENT WITH MULTIPLE FRACTURES OF THE THORACIC AND LUMBAR VERTEBRAE ASSOCIATED WITH HAJDU – CHENEY SYNDROME

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A clinical case of surgical and multimodal conservative treatment of an 11-year-old female patient with Hajdu – Cheney syndrome with multiple vertebral fractures in the thoracic and lumbar spine is presented. The main and significant manifestations of this syndrome are osteoporosis and acroosteolysis. After the injury, the child underwent correction of posttraumatic spinal deformity and stabilization of spinal motion segments by a placement of multi-anchor instrumentation through a posterior approach. The long-term postoperative period was characterized by the absence of bone block formation, development of distal junctional kyphosis and scoliotic deformity, which required additional surgical intervention in the amount of elongation of instrumentation and correction of the developed curvature. The paper describes in detail the clinical manifestations of the syndrome, the results of surgical treatment, and clinical and radiological characteristics.
Key Words: Hajdu – Cheney syndrome, unstable spine fracture, vertebral compression fracture, acroosteolysis, osteoporosis.
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The Hajdu – Cheney syndrome is a rare autosomal dominant genetic disorder. This symptom complex was first described by Hajdu and Kauntze in 1948 as a manifestation of cranio-skeletal dysplasia; acro-osteolysis was added to the disease description in 1965 [1].

The syndrome is caused by heterozygous mutations in the NOTCH2 gene [2]. The signal encoded by this gene is considered one of the main signaling pathways regulating a broad range of vital processes in embryogenesis. Therefore, it is no wonder that mutations in the gene encoding NOTCH receptors or ligands cause various congenital disorders. Simultaneously, the data on sporadic cases of the Hajdu – Cheney syndrome development have been reported [3].

The syndrome is also known as the acro-osteolysis syndrome, arthro-dento-osteo dysplasia, hereditary osteodysplasia with acro-osteolysis, cranioskeletal dysplasia with acro-osteolysis, and familial osteodysplasia. A total of 122 patients having this pathology are known worldwide. Detailed description of surgical management of spinal fractures in a patient having this syndrome was given in only one publication. No studies analyzing the outcomes of treatment in pediatric patients having the Hajdu – Cheney syndrome have been revealed among Russian-language literature.

The Hajdu – Cheney syndrome has an early childhood onset and is characterized by progression and aggravation of clinical signs during child's growth and development. The key manifestation are acro-osteolysis, osteoporosis, and craniofacial anomalies.

Other typical traits of the pathology related to the skeletal system include short stature of a child, long bone deformities (s-shaped fibular bone), joint hypermobility, short broad fingers, and spinal deformity (scoliosis, kyphosis). The traits related to the cranial bones and facial structure include platybasia, micrognathism, non-closing cranial sutures, basilar invagination, epactal bones, synophrys, hypertelorism, abnormalities of tooth structure, premature loss of teeth, and epicanthus. Features related to other organs and systems may include polycystic kidney disease, neurological disorders caused by basilar invagination (ranging from pyramidal insufficiency to spastic tetraparesis), sensorineural hearing loss, congenital malformations of the cardiovascular system, and hirsutism [4, 5]. In addition to the aforementioned typical manifestations of the syndrome, when analyzing case reports available in the world literature, the researchers also focus on instability and destruction of interphalangeal joints, syringomyelia, hydrocephalus, dural ectasia, sensorimotor polyneuropathy, Arnold – Chiari malformation, splenomegaly, interventricular septal and atrial septal defects, coarctation of the aorta, chronic kidney failure, and vesicoureteral reflux. It should be emphasized that it is extremely unlikely that one patient has all of these symptoms.

The key methods for treating patients with Hajdu – Cheney syndrome include medication therapy and surgical interventions [6]. However, there is no evidential basis for conservative treatment with anabolic drugs and bone resorption inhibitors. Simultaneously, any surgical intervention for bone or joint deformities in these patients is associated with a high risk of complications and recurrence, since it is anticipated that post-

operative bone consolidation will take a long time in patients with conditions typical of the Hajdu – Cheney syndrome (e.g., acro-osteolysis, osteoporosis, and collagen anomalies) and that there will be problems related to soft tissue healing.

The objective of this study was to analyze the diagnosis and treatment of a patient having the rare autosomal dominant skeletal disorder accompanied by multiple fractures of vertebral bodies in the thoracic and lumbar spine.

A 7-year-old female patient S. was admitted to the clinic of the Turner Scientific Research Institute for Children's Orthopedics (St. Petersburg, Russia) in 2014. The patient complained of thoracic spine pain radiating to the lumbar spine. The medical record indicates that the child was injured as she fell from an exercise ball. Patient's diagnosis at admission was burst fracture of the T5 vertebral body, compression fractures of the T3, T8, and L3 vertebrae, spinal stenosis at the T5 level.

The orthopedic status at admission was as follows: a girl with the asthenic constitutional type and proportional body shape, unable to walk independently because of severe pain; the thoracic kyphosis was exaggerated and lumbar lordosis was smoothed. The spinal axis in the thoracic and lumbar regions was not deformed. Palpation of spinous processes of T3, T5, T8, and L3 vertebrae identified expressed tenderness.

Physical examination revealed some phenotypic traits: short height, joint hypermobility, epicanthic fold, hypertrophic osteoarthropathy, thick eyebrows, coarse hair, and a long philtrum.

Spinal radiograms and MR images showed local kyphosis at the T5 vertebral level, no lumbar lordosis, a burst fracture of the T5 vertebra, compression fractures of the T3, T8, and L3 vertebrae, and spinal stenosis at the T5 level (Fig. 1).

Neurological examination revealed no neurological symptoms.

Radiological examination revealed reduced density and rarefication of the bone tissue within vertebral bodies. Hence, densitometry was carried out to evaluate bone tissue density, which revealed that bone mineral density was reduced by 13 % throughout the entire skeleton and by 28 % in the lumbar spine.

Taking into account that the patient had severe spine injury, mechanical instability at the level of T5 burst fracture, imminent neurological instability at the injury site, and spinal stenosis, a decision was made to conduct emergency surgery. The intervention through the dorsal approach involved correction of post-traumatic deformity, elimination of spinal stenosis, and stabilization of the injured spinal motion segment using transpedicular fixation with instrumentation system in combination with local posterior fusion.

Bone canals were formed in the T4, T6, and T7 vertebral bodies on either side of the line of the spinous processes to insert anchoring elements of the instrumentation system; markers were placed; and two-view X-ray control was performed. Six transpedicular screws were inserted into the formed canals. This length of fixation was selected so that it overlapped the area of physiological kyphosis. Since the injuries to the T3 and T8 vertebral bodies were of compression type only within the anterior vertebral column, spinal canal was not narrowed at this level. Therefore, there was no need to include this level into the area exposed to fixation. Furthermore, it was planned that the patient would wear a rigid hyperextension thoracolumbar brace to deload the compressed thoracic and lumbar vertebrae [7]. Two rods bent and contoured to follow the shape of physiological thoracic kyphosis were placed into the anchoring elements and fixed with locking nuts. The post-traumatic deformity in the thoracic spine was corrected and the thoracic kyphosis was restored. Repositioning of the injured zone was achieved; the physiological spine curvature was restored; and spinal stenosis was eliminated. Local posterior fusion using autobone graft at the T4–T7 level was performed at the final step of the intervention. No neurological impairment was observed postoperatively.

During the postoperative period, the patient received antibiotics for seven days, hemostatic therapy (dicynone) for two days, analgesics, and infusion therapy. The child was verticalized three days after the surgery. Taking into account that the child had multiple compression fractures in the thoracic and lumbar spine, a custom-made rigid plastic hyperextension brace was manufactured for her. It was recommended that the patient would wear this brace for 18 hours during the day [7]. Adaptation to wearing the brace took three days. The patient was discharged from the hospital on day 7 post-surgery.

After the surgery, the child was receiving conservative treatment: restricted orthopedic regime (no sitting position was allowed), physical therapy aimed at strengthening back and abdominal muscles, wearing the rigid functional correcting brace, and swimming that could be started 4 months after the surgery. Because of low bone mineral density revealed by densitometry, the main course of conservative treatment was accompanied by bisphosphonate therapy (once per 3 months through i.v. infusion) during two years, followed by cycles once per six months.

Taking into account the child's phenotypic traits, the suspected systemic nature of the disease, and the multiple fractures of vertebral bodies that resulted from a low-energy injury, it was recommended that the patient should be examined at the medical genetics center. After a consultation with a geneticist, with allowance for the combination of specific external signs, the typical clinical presentation, and the genetic findings, the child was diagnosed with the Hajdu – Cheney syndrome. In this case, the pathology was familial, since the girl's mother was also diagnosed with the syndrome. She had the characteristic clinical and phenotypic traits: hypertrophic arthropathy, acro-osteolysis, osteoporosis, and facial signs.

The child had no complaints at control examination six months after the surgery. The spinal axis was of regular shape; the sagittal profile was near-physiological. The pectoral girdles lay on the same line; waist triangles were symmetrical; no pelvic distortion was observed. During the treatment, frontal and lateral radiograms of the spine visualized cor-

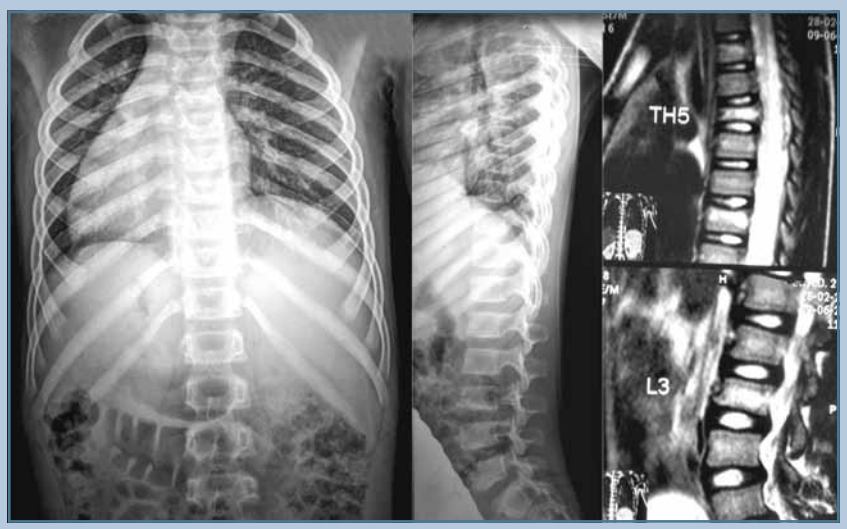

Fig. 1
Spinal radiograms and MR images of the 7-year-old patient S. having a burst fracture of the T5 vertebra and compression fractures of the T3, T8, and L3 vertebrae

rect and stable position of the instrumentation system at the level of T4–T7 vertebrae (Fig. 2). In the frontal plane, the axis of the thoracic spine slightly deviated towards the right side. In the sagittal plane, physiological thoracic kyphosis and physiological lumbar lordosis were observed. No spinal stenosis at the level of T5 vertebra was visualized. The height of L3 vertebral body was restored, while the height of the anterior column of the T8 vertebral body was reduced.

The absence of patient's complaints, the steady-state clinical presentation, adequate positioning of the instrumentation, and restoration of the L3 vertebral body height (after wearing a rigid hyperextension brace) gave grounds for continuing the conservative treatment and performing dynamic follow-up. During the subsequent three years, control clinical and radiological examination revealed no negative dynamics. The child was receiving conservative treatment (physical therapy daily, massage of the collar zone and lumbar region (4 sessions per year), and swimming). One year after the surgery, the restricted orthopedic regime was expanded: the patient was allowed to sit. One and a half years after the surgical intervention, wearing the rigid hyperextension brace was terminated. The child was subjected to densitometry once a year. Despite the bisphosphonate therapy, the densitometry data remained below normal: in 2015, bone mineral density in L1–L4 vertebrae was 33 % lower than the value anticipated for this age; in 2016–2017, lower by 24 %.

In mid-2018 (four years after the surgery), a routine control examination revealed that the clinical presentation of the disease was significantly worsened. The girl had no major complaints, but the following features of the orthopedic status were observed: the right pectoral girdle was lifted higher than the left one; the spine axis deviated towards the right side in the thoracic region and towards the left side at the thoracolumbar junction; the angle of the right scapula was higher than that of the left scapula by 2 cm; waist triangles were asymmetrical (the right one being deepened and the left one being flattened); the Adams test revealed gibbus costalis (2 cm); thoracic kyphosis in the sagittal profile was aggravated.

The radiological and CT data demonstrated that position of the instrumentation system and transpedicular support elements in the T4, T6, and T7 vertebral bodies was stable and adequate on both sides. It was observed that height of the L3 vertebral body was restored and height of the T5 vertebral body increased as compared to radiograms recorded in 2014. An abrupt decrease in height of the anterior column of the T8 vertebral body and distal junctional kyphosis below the inserted instrumentation system were also revealed. The Cobb angle of the right thoracic scoliotic curve at the T3–T10 level was 25°; the Cobb angle of the left thoracolumbar curve at the T11–L3 level was up to 21°. The Cobb angle of thoracic kyphosis became 54°. No bone block was formed along the spinal instrumentation system (Figs. 3, 4).

Densitometric study revealed that bone mineral density of the L1–L4 vertebrae was 18 % lower than the age-appropriate normal value. Hence, the conservative treatment was accompanied by positive dynamics: the bone tissue density increased.

The clinical and radiological presentation observed 4 years after the surgery was most likely related to the child's growth spurt (the girl's height gain over the past year was 6 cm) and the placed instrumentation system. The instrumentation prevented restoration of the body height of the injured T8 vertebra during conservative treatment and even worsened its condition because of intense load on the lower spinal motion segment. Furthermore, the absence of posterior bone block along the instrumentation system has also contributed to the clinical presentation.

Taking into account the child's age, the presence of scoliotic deformity, and the absence of restoration of the T8 vertebral body height and progressive distal junctional kyphosis below the level of instrumentation (as well as the posterior bone block) after surgical treatment, a decision was made to conduct stepwise spinal reconstruction.

The girl was hospitalized and subjected to surgical intervention that involved stepwise correction of spinal deformity, placement of additional anchoring elements of the instrumentation system below the level of distal junctional kyphosis, correction of the existing

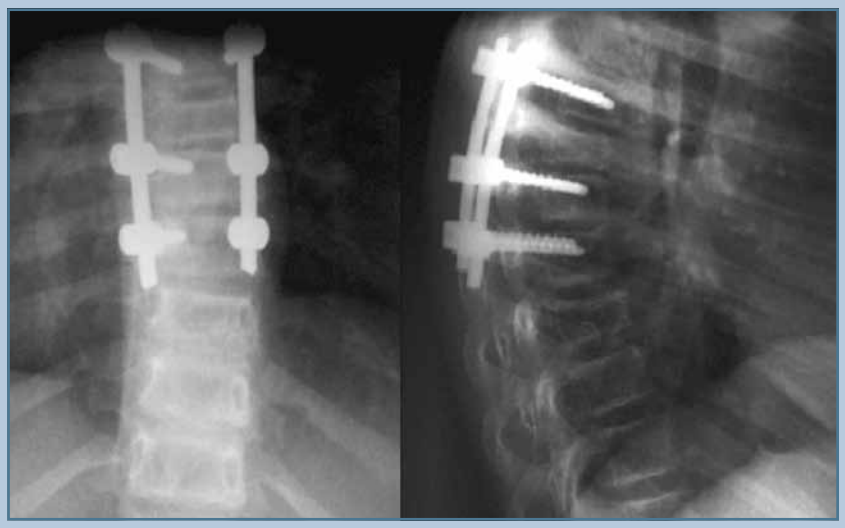

Fig. 2
Frontal and sagittal radiograms of the spine of the 7-year-old patient S. 6 months after the injury

deformity, and formation of an additional bone block. A complete preoperative examination was carried out.

During the surgical intervention, additional transpedicular anchoring elements were inserted into the T9 vertebral body on two sides with respect to the central line of spinous processes. The posterior multi-anchor instrumentation system was replaced with allowance for child's age and weight. A total of eight anchoring elements of the instrumentation system were inserted. Rods bent and contoured to follow the shape of physiological spine curvature were coupled into these anchoring elements. The existing deformity was corrected and the achieved results were stabilized. The final step of the intervention involved local posterior fusion using autobone graft (Fig. 5).

After the surgical treatment, the Cobb angle of thoracic kyphosis was improved to 34°; the Cobb angle of the residual right thoracic scoliotic curve (T3–T10) became 7°; the Cobb angle of the left lumbar curve (T11–L4) was improved to 9°. The surgery was uncomplicated; the child was verticalized on day 3 after the intervention. A custom-made spinal brace was manufactured on day 7, and the patient was discharged in a stable condition.

Eight months after surgical treatment, patient's clinical presentation showed no negative dynamics. The control radiograms demonstrated stable position of the instrumentation system and no loss of the achieved correction.

Discussion

The Hajdu – Cheney syndrome is a rather rare disease. Its clinical presentation includes various dysmorphic craniofacial features and musculoskeletal abnormalities. In all cases, the entire complex of symptoms results from the abnormal connective tissue development during the embryonic period.

According to the literature data [8], mutation in the NOTCH gene and loss of protein function results in the Adams–Oliver syndrome, Alagille syndrome, spondylocostal dysostosis, and congenital heart defects. The mutation inducing hyperexpression of the encoded protein causes the Hajdu – Cheney syndrome, polycystic kidney disease, infantile myofibromatosis, and lateral meningocele syndrome.

The recent studies [2] have demonstrated that aberrant Notch2 signaling and the subsequent osteoclastic hyperactivity are tightly related to the pathogenesis of this bone disorder, but its accurate molecular mechanisms are still to be elucidated. The steady-state osteoclastic hyperactivity is largely caused by accumulation of carboxyl terminus-truncated Notch2, which accelerates ubiquitination and degradation of Notch2 protein.

Mouse experiments have demonstrated that bone tissue loss is a process secondary to increased osteoclastogenesis and bone resorption due to enhanced expression of the receptor activator of nuclear factor kappa-b ligand (Rankl) of Notch2.

In the skeletal mesenchyme, Notch2 negatively regulates differentiation of mesenchymal precursors into osteoblasts; osteoblast ablation causes gradual loss of bone mass loss in adult mice [9].

The questions regarding pathogenetic treatment of this syndrome, prevention of its development and early prenatal diagnosis remain open. The existing conservative treatment and surgical methods are only symptomatic and, as already mentioned earlier, are not evidence-based.

Anabolic treatment with teriparatide and bisphosphonates is currently used to treat osteoporosis in patients with Hajdu – Cheney syndrome; however, indubitable data that would indicate that this treatment is effective are not available. Teriparatide increases bone mineral density in patients with this syndrome; however, it has not been revealed whether or not bisphosphonates and teriparatides prevent recurrent fractures. The positive effect of osteoporosis treatment with bisphosphonates in patients with this syndrome decreases with age; no data on the effect of these medications on acro-osteolysis are available thus far [10].

Surgical treatment is challenging because of severe osteoporosis. Our case report illustrates this fact. An uncomplicated spinal fracture required multistage surgical treatment because of the long-lasting bone block formation and development of distal junctional kyphosis caused by altered bone density during

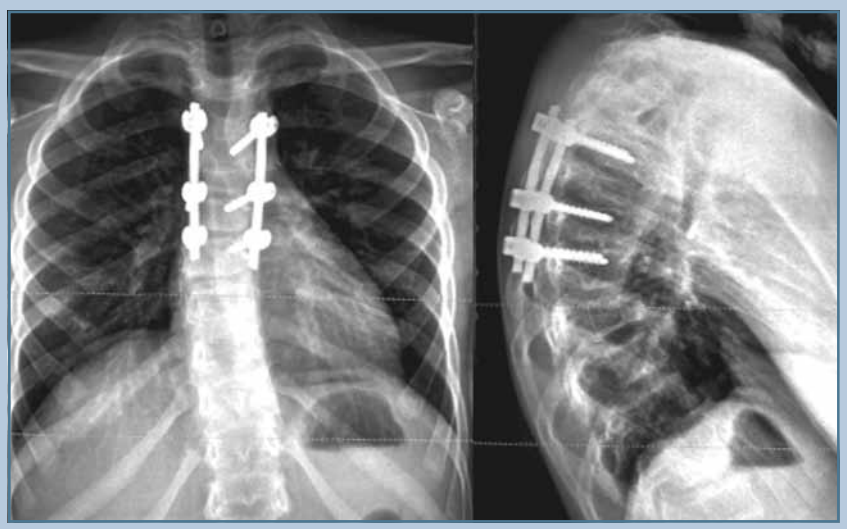

Fig. 3
Frontal and sagittal radiograms of the spine of the 11-year-old patient S. four years after the injury: distal junctional kyphosis and scoliotic spinal deformity

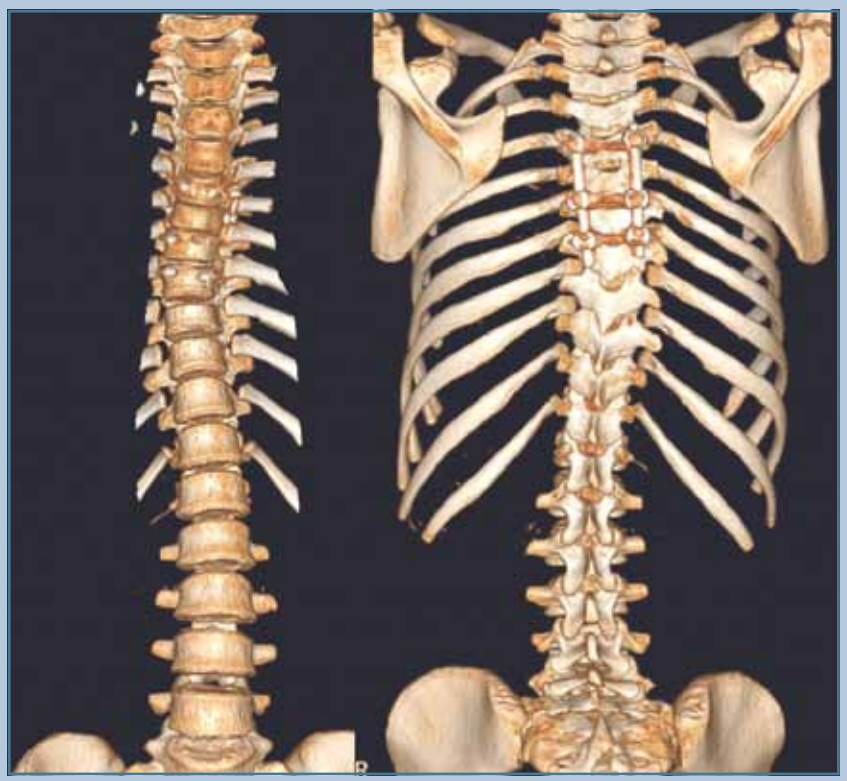

Fig. 4
CT scan of the spine of the 11-year-old patient S. four years after the injury: distal junctional kyphosis, scoliotic spinal deformity, no bone block was formed along the instrumentation system

osteoporosis, although the patient was receiving background conservative treatment with bisphosphonates.

Conclusions

In pediatric patients with Hajdu – Cheney syndrome, multiple and severe spinal fractures can occur even after a minimum energy impact.

Treatment of unstable spinal fractures in patients with this syndrome is a serious challenge. The surgical intervention can be complicated by failure of bone block formation in the operated area and deformity progression as the child grows, especially if there are multiple fractures of vertebral bodies. Disorders of the metabolism of osseous and connective tissue, which are typical of this syndrome, may result in loss of the achieved correction in late postoperative period and require stepwise surgical treatment.

When performing surgical treatment of patients with Hajdu – Cheney syndrome, one needs to pay special attention to the features of disorders of the osseous and connective tissue structure, as well as on the effect of these disorders on the course of postoperative period.

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The authors declare that there is no conflict of interest.

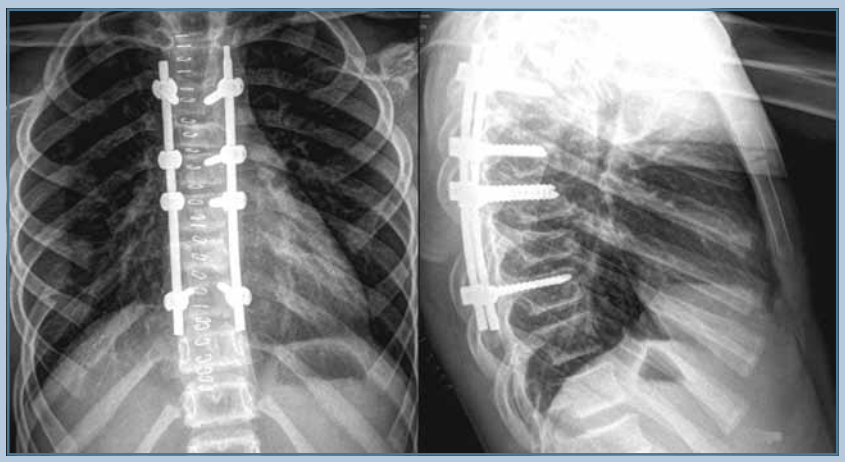

Fig. 5
Frontal and sagittal radiograms of the spine of the 11-year-old patient S.: the outcome of correcting and stabilizing the scoliotic spinal deformity and distal junctional kyphosis by placing multi-anchor instrumentation

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