

WERNER MESOMELIC DYSPLASIA

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Introduction. The term “mesomelic dysplasia” refers to a group of disorders wherein limb shortening is most pronounced in the middle segment (forearm and leg) of the extremities. Werner mesomelic dysplasia is characterized by absence or hypoplasia of the tibia, preaxial polysyndactyly on the hands and feet, as well as by triphalangeal thumbs, absence of a patella, and fibular bone dislocation. Molecular genetic causes of the disease are mutations at position 404 of the regulatory element (ZRS) of the *SHH* gene in the *LMBR1* gene (OMIM 188740).

Clinical case. A girl with triphalangeal thumbs and polydactyly of the hands, right hip dislocation, tibia hypoplasia, fibular dislocation on both sides, and preaxial polydactyly of the feet was examined and treated at the age of 1 year. Considering the clinical and radiological picture, the girl was diagnosed with Werner mesomelic dysplasia. To verify the disease, a molecular genetic examination of the child was performed. A variant of replacement of 230 T>C in the regulatory element of the ZRS of the *SHH* gene was discovered in the literature.

Discussion. Differential diagnosis can be made with Laurin-Sandrow syndrome, which is characterized by doubling of the ulna and fibula with the absence of the radius and tibia and preaxial polydactyly/syndactyly of the hands and feet. The presence of nasal defects (particularly involving the columella) distinguishes this condition from other syndromes, which was not shown in this clinical observation.

Conclusion. We report the clinical case of an autosomal-dominant disease, Werner mesomelic dysplasia, which is a rare pathology with a typical clinical picture combined with congenital hip dislocation, which was not previously described. The molecular genetic examination confirms the presence of a pathogenic variant of the ZRS element of the *SHH* gene, which causes the development of Werner’s mesomelic dysplasia, but the mutation variant was not registered before, which requires an additional examination of the child’s relatives.

Keywords: Werner mesomelic dysplasia; hypoplasia of the tibia; preaxial polysyndactyly; triphalangeal thumbs; absence of a patella; dislocation of the fibula bones.

МЕЗОМЕЛИЧЕСКАЯ ДИСПЛАЗИЯ ВЕРНЕРА

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Введение. Мезомелические дисплазии представляют собой гетерогенную группу заболеваний с укорочением конечностей преимущественно в среднем сегменте (предплечье, голень). Мезомелическая дисплазия типа Вернера характеризуется отсутствием или гипоплазией большеберцовой кости, преаксиальной синполидактилией на кистях и стопах, а также трехфалангизмом первого пальца кисти, отсутствием надколенника и вывихом малоберцовой кости. Молекулярно-генетической причиной заболевания являются мутации в положении 404 регуляторного элемента (ZRS) гена *SHH*, находящегося в интроне 5 гена *LMBR1* (OMIM 188740).

Описание клинического случая. Под нашим наблюдением находится девочка с трехфалангизмом и полидактилией первых пальцев обеих кистей, вывихом правого бедра, гипоплазией большеберцовых костей с двух сторон, вывихом малоберцовых костей, преаксиальной полидактилией и полифалангией на стопах. С учетом клинико-рентгенологической картины поставлен диагноз: «мезомелическая дисплазия Вернера». Для верификации заболевания выполнено молекулярно-генетическое обследование ребенка, при этом обнаружен неописанный в литературе вариант замены 230 T > C в регуляторном элементе ZRS гена *SHH*.

Обсуждение. Дифференциальный диагноз возможно провести с синдромом Laurin-Sandrow, который включает в себя удвоение локтевой кости и малоберцовой кости с отсутствием лучевой и большеберцовой костей,

преаксиальную поли/синдактилию кистей и стоп. Наличие назальных дефектов отличает данное состояние от других синдромов, что не было выявлено в данном клиническом наблюдении.

Заключение. Описание приведенного клинического случая аутосомно-доминантного заболевания мезомелической дисплазии Вернера сделано с целью демонстрации редкой патологии с характерной клинической картиной, сочетающейся с врожденным вывихом бедра, что ранее не было описано. Молекулярно-генетическое обследование подтверждает наличие патогенного варианта элемента ZRS гена *SHH*, которое обуславливает развитие мезомелической дисплазии Вернера, однако вариант мутации не зарегистрирован ранее и требует проведения дополнительного обследования родственников ребенка.

Ключевые слова: мезомелическая дисплазия Вернера; гипоплазия большеберцовой кости; преаксиальная син-полидактилия; трехфалангизм первого пальца кисти; отсутствие надколенника; вывих малоберцовой кости.

Mesomelic dysplasia is a heterogeneous group of diseases with shortening of the extremities, mainly in the middle segment, such as the forearm and shin [1–3]. The characteristic signs of Werner type dysplasia include the absence or hypoplasia of the tibia, preaxial synpolydactyly on the hands and feet, triphalangism of the thumb, and the absence of the patella and dislocation of the fibular bone [4, 5]. As a rule, the lesion is bilateral and asymmetrical. The first clinical case of this disease was presented in 1915 by the German obstetrician-gynecologist P. Werner who described a 20-year-old pregnant woman with a sharp shortening of the lower legs, aplasia of the tibia, with six-fingered hands and doubled three-phalanx thumbs, with seven and eight toes [4].

Several familial cases described in the literature indicate an autosomal dominant mode of inheritance with variability of the disease signs [3, 5–12]. For instance, Lamb, Wyenn-Davies, and Whitmore (1983) described 15 cases across five generations of preaxial polydactyly of the hands and feet that were associated with partial or complete absence of the tibia. According to the authors, a five-fingered hand with a three-phalanx finger and synpolydactyly of the great toe on both the sides were observed among all family members. The complete absence of the tibia was detected in four patients, of which three had bilateral lesions. Proximal migration of the head of the fibula and its hypertrophy and hypoplasia of the distal part of the femoral bone was noted in all patients. Three of them had agenesis of the lower third of the radial bone, which was unilateral in one case and bilateral with hypertrophy, migration, and valgus deformity of the ulnar bone in two cases.

Some past analyses has revealed that, in recent years, increasing number of publications prove the genetic nature of the disease [3, 13–15]. According to the literature, the molecular genetic cause is a mutation at the position of the regulatory sequence 404 (ZRS) of *SHH* located in *LMBR1*.

ZRS is a regulatory sequence responsible for the initiation and spatial orientation of *SHH* expression in the zone of the polarization activity of the limb development. Mutations in the regulatory sequence of the *SHH* are described in type 2 preaxial polydactyly, type 4 syndactyly, and triphalangism of the thumb in combination with syndactyly. In 2010, a paper reported two unrelated patients diagnosed with Werner type mesomelic dysplasia had two mutations, point replacements $G > A$, $G > C$ in position 404 of the ZRS of *SHH* [16]. Fedotov et al. (2013) analyzed the family observation of Werner type mesomelic dysplasia with molecular genetic verification. Simultaneously, the replacement $T > G$ was detected in the conservative position 403 of the ZRS of *SHH* located in *LMBR1*. In patients with the same mutation and even in those of the same family, a different degree of lesion to the tibial bones was observed. Replacement not only in the 404 ZRS position but also, possibly, in the surrounding region of this nucleotide, in addition to preaxial polydactyly and the triphalangism of the thumb, lead to the development of the lesion of the tibial bones and Werner type mesomelic dysplasia [17].

Description of the clinical case

A girl aged 5.5 years under our observation had multiple malformations of the upper and lower extremities. Anamnesis revealed that the child was derived from a third pregnancy and third birth. Family history of hereditary orthopedic pathology was not burdened. The parents of the child are healthy, and the couple is unrelated. In the early stages of the mother's pregnancy, fluorography and vaccination (including tetanus, diphtheria, and pertussis) were performed. The job profile of the mother was associated with hazardous production (i.e., lead vapor generation). Although the pregnancy proceeded without toxicosis, at 24th week of gestation, ultraso-

nography detected shortening of the child's lower legs. At 38th week, the child was born via cesarean section, and the child was in pelvic presentation with a birth weight of 3550 g. At the first clinical examination at the age of 1 year and 1 month, the child showed normosthenic body type with satisfactory nutrition. She could sit independently, but did not walk. The head was of the correct shape and located in the midline. The spinal axis was straight. Movement in the shoulder, elbow, and wrist joints were not limited and painless. The right and left hands were represented by six rays, of which rays 2–5 developed normally. The first ray of the right hand was doubled, each of which was represented by metacarpal bones and three-phalangeal fingers in syndactyly. On the left hand, the first ray was doubled, represented by two three-phalangeal fingers and metacarpal bones. Hypoplastic metacarpal and the main, middle, and nail phalanges were noted in the radial additional ray. There is no opposition of the first rays of the hand. On the side of the lower extremities, the shortening of the right lower extremity by 1 cm was notable. The abduction and flexion of the hip joints were not limited. Excessive external rotation in the hip joints, on the right to a greater extent, was revealed. Valgus deformity at the level of the right knee joint was noted. Flexion in the knee joints was complete on both the sides, with extension on the right up to 160° and on the left being complete. Pathological mobility of the knee joints in the frontal plane was possible. The feet were in the supination-varus position. The right foot was represented by seven rays (preaxial polydactyly). Two additional rays were represented by metatarsal bones and three-phalangeal toes. The left foot is represented by eight rays (i.e. preaxial polydactyly and polyphalangism). The first ray was represented by the metatarsal bone, the main phalanx, and the doubled nail phalanx located in syndactyly. At the first additional ray, metatarsal bone aplasia and hypoplasia of the main phalanx were noted. The middle and nail phalanges developed normally. The other two additional rays were represented by normal metatarsal bones and normally developed three-phalangeal fingers (Figs. 1, *a–c*).

The radiological examination of the hands revealed triphalangism with polydactyly (a dolichophalangeal form of triphalangism). The radiograph of the spine showed no pathology. The child also showed a dislocation of the right hip, hypoplasia of

the tibial bones on both the sides, dislocation of the fibular bones, preaxial polydactyly, and polyphalangism on the feet (Figs. 1, *b, d–f*). Considering the clinical radiological pattern, the diagnosis of Werner type mesomelic dysplasia was established.

Conservative treatment of hip dislocation was performed using the Koszla splint for 3 months and then the Mirzoyeva splint. Concentric reposition of the right hip head into the cavity was thereby achieved. After 4 years of the conservative treatment, the joint is presently clinically and radiologically stable (Fig. 2, *e*).

In 2013, at the age of 1 year and 1.5 years, the pollicization of the first ray was performed and the additional ray was removed in stages on the right and left hands. Then, in 2014, at the age of 1 year 10 months and 1 year and 11 months, polydactyly on the right and left feet was eliminated. In 2017, during an examination, shortening of the left lower limb by 5 cm, valgus deformity of the right lower limb, and gait disturbance were noted in the child (Figs. 2, *a, c, d, f*). Presently, the hands and feet are represented by five rays. The bilateral gripper function of the hand is satisfactory (Fig. 2, *b*). A multi-stage surgical treatment was planned to correct the deformities and different lengths of the lower limbs.

To verify the disease, a molecular genetic examination was performed. A search for mutations in the ZRS of *SHH* was conducted by the Sanger sequencing method. Pathogenic variants of this sequence cause the formation of tibial hypoplasia with polydactyly (OMIM 188740). However, our analysis also revealed a variant of the uncertain clinical value of replacement 230 T > C, which has not been described in the literature. In order to determine the possible origin of the *de novo* mutation and segregation with the disease, additional examinations of genetical relatives are presently being planned.

Discussion

The group of mesomelic dysplasias includes diseases such as dyschondrosteosis, Nivergelt mesomelic dysplasia, Langer mesomelic dysplasia, Robinson mesomelic dysplasia (fetal facial syndrome), Reinhardt dysplasia, and Werner dysplasia [18]. Werner type dysplasia differs from other mesomelic dysplasias or syndromes with polysyndactyly due to the presence of preaxial polydactyly with triphalangism of the first finger and agenesis of the tibia. The wide family variability is typical, although in

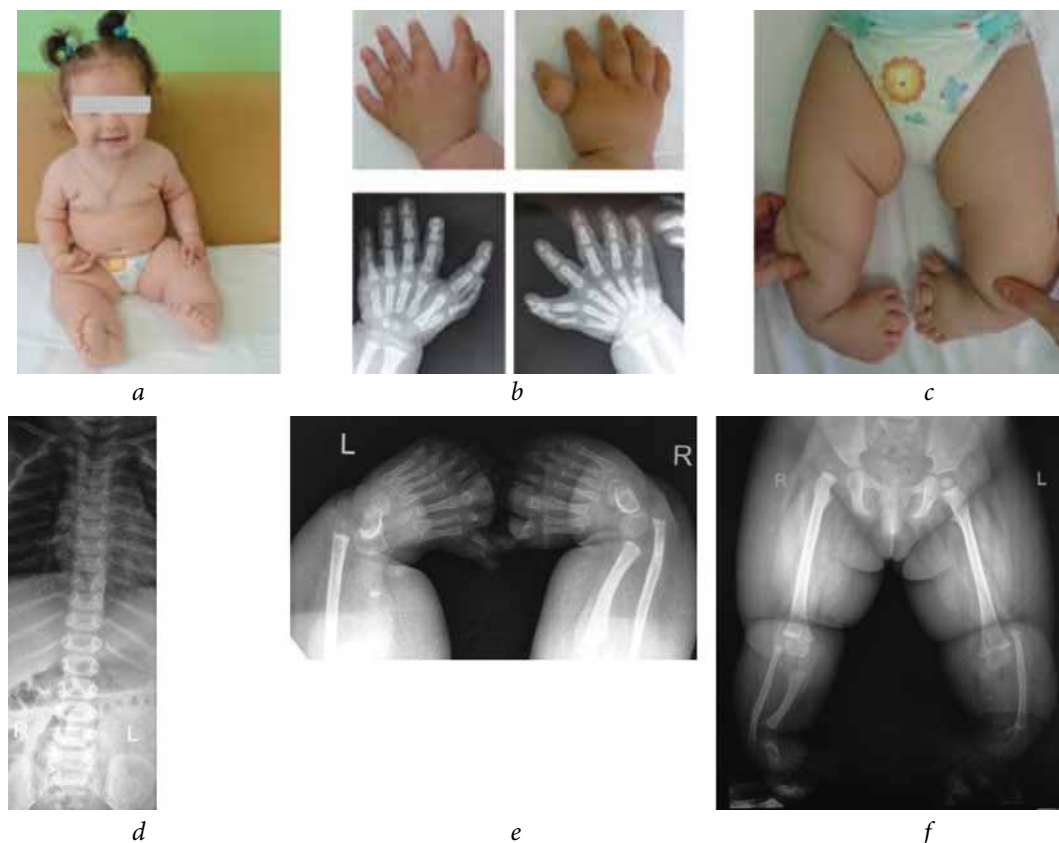


Fig. 1. Patient J., before surgery: *a* — patient's appearance; *b* — the appearance and radiographs of the hands; *c* — the appearance of the lower extremities; *d* — radiographs of the spine; *e* — radiographs of the feet; *f* — radiographs of the lower extremities

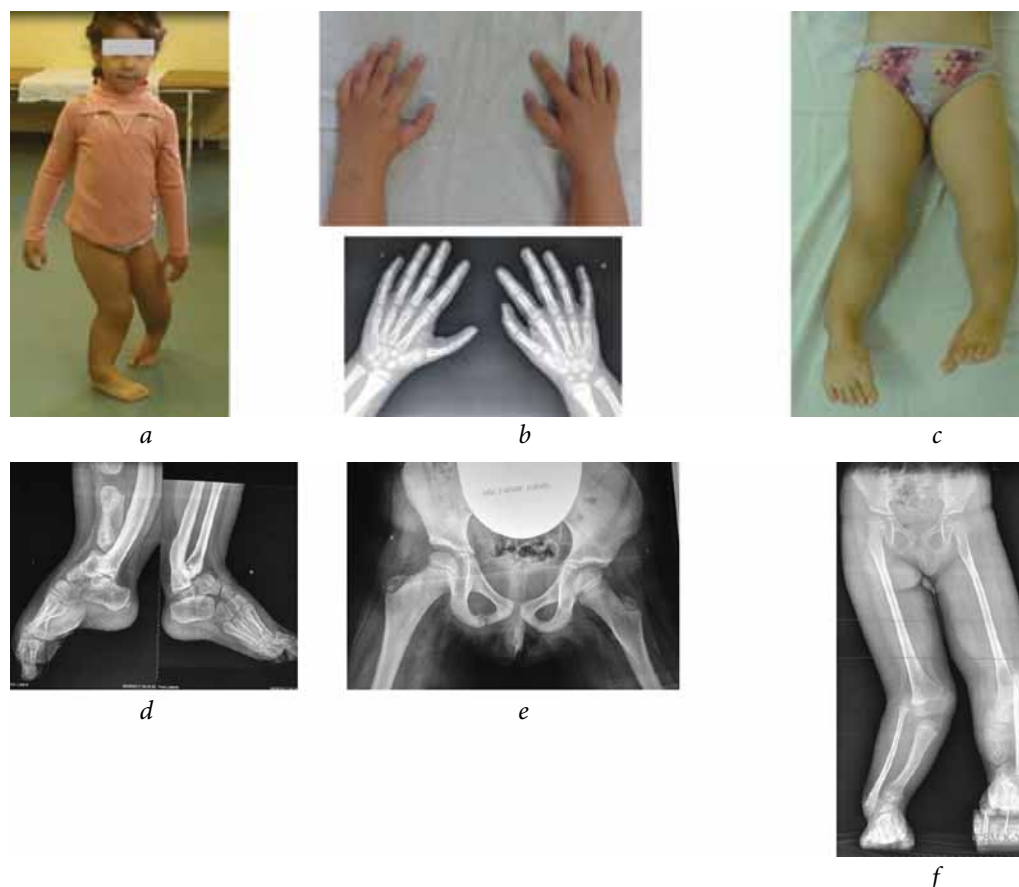


Fig. 2. Patient J., 5.5 years (3 years after surgery): *a* — the patient's appearance; *b* — the appearance and radiographs of the hands; *c* — the appearance of the lower extremities; *d* — radiographs of the feet in the lateral projection; *e* — radiographs of the hip joints; *f* — panoramic radiograph of the lower extremities standing with compensation of shortening

some cases, only triphalangism of the first finger has been reported [3, 5]. Several authors indicate autosomal dominant mode of inheritance; however, Temtamy and McKusik (1978) described the typical clinical manifestations in a child whose parents were healthy, but some family members on the father's side showed similar deformities [19]. Sporadic cases of the disease have been described in the literature [9].

In addition, the published articles describe clinical family cases with a typical set of signs that are characteristic of Werner type dysplasia, although the diagnosis was not mentioned [20].

A differential diagnosis may be conducted with the mirror hand syndrome. The Laurin–Sandrow syndrome (mirror hand syndrome) includes doubling of the ulna and fibula, with no radial and tibial bones and preaxial poly/syndactyly of the hands and feet, often of the mirror type [21–27]. For Laurin-Sandrow syndrome, polydactyly is typical both in an isolated version and as a part of the syndrome, although mirror type polydactyly on the feet is quite rare. Laurin et al. and Sandow described the polydactyly on the hands, the mirror type polydactyly on the feet in combination with the defect of the nose, especially in the area of the columella [28]. The disease has an autosomal dominant mode of inheritance, although sporadic cases may reflect *de novo* mutation. The presence of nasal defects distinguishes this condition from other syndromes, which was not revealed in this clinical case.

Conclusion

The description of the present clinical case of Werner type mesomelic dysplasia demonstrates a rare pathology with tibial hypoplasia and polydactyly, presenting with congenital hip dislocation; such a case has not been described previously in the literature. Molecular genetic testing has confirmed the presence of a pathogenic variant of the ZRS of *SHH*, which leads to the development of Werner type mesomelic dysplasia, although the mutation variant has not been previously registered, which requires an additional examination of the child's blood relatives.

Additional information

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Ethical review. The parents of the patient agreed to the processing of personal data and their publication.

Contribution of authors

E.A. Kochenova was involved in supervision, surgical treatment of the patient, analysis of literary sources, collection of material, and preparation of the article text.

O.E. Agranovich performed editing of the article, surgical treatment of the patient.

S.I. Trofimova performed the analysis of literary sources, the preparation of the text, and editing of the article.

A.P. Nikitina helped in organizing a genetic testing, analysis and interpretation of its results.

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