THE NEW ARMENIAN MEDICAL JOURNAL
Vol.14 (2020), No 3, p.52-59

PSYCHOLOGICAL PROBLEMS OF CHILDREN WITH GENETIC OSSIFICATION OF SOFT TISSUES

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Receive 22.02.2020 d; accepted for printing 14.07.2020

Abstract

The article discusses the psychological problems of children with rare genetic diseases of an autosomal dominant nature – fibrodysplasia ossificans progressiva and progressive osseous heteroplasia. The diseases are accompanied by ossification and/or calcifications of soft connective tissue mass outlined among various congenital bone and articular abnormalities. Inevitably developing contractures of joints adjacent to ossificates and calcifications on the spinal cord lead to limited mobility up to the patient's partial or complete inability to perform self-care. Along with the commonly found acquired skeletal deformities that change the appearance, they cause psychological disorders, thus becoming an obstacle to the successful integration of a child in society. In this regard, the life quality of these patients is being addressed. The authors share their experience in attempts to solve the psychological problems of patients, having 33 children under supervision (among them 28 children with fibrodysplasia ossificans progressiva and 5 children with progressive osseous heteroplasia). The issues of the future professional choice of adolescents are raised. The attitude towards these patients in the family is described. The article also describes new psychological problems between a doctor and parents, resulting from a possible preclinical diagnosis of these genetic diseases. The absence of etiotropic, pathogenetic therapy, even symptomatic treatment with proven effectiveness, also aggravates the psychological problems, giving rise to despair or unreasonable expectations of patients. It is also highly important to focus on the discussion of the psychological state of parents who face a very difficult choice whether to have other children or not, for the risk of a recurrence of congenital pathology, or for the fear of potential challenges in the relationship of future children. The article substantiates the necessity of close interaction of doctors – pediatricians, rheumatologists, orthopedists, geneticists with psychologists in search of joint solutions of psychological problems in the family with a child who has a rare disabling genetic pathology.

Keywords: *fibrodysplasia ossificans progressiva, progressive osseous heteroplasia ossificates, life quality, children, psychological problems.*

Introduction

The end of the 20th century and the two decades of the 21st century are characterized by significant achievements in scientific and practical medicine. A new concept such as "quality of life" has appeared in assessing the patient's condition.

There is no common definition of the term "life quality of a patient". Life quality of a person is an evaluative category that summarizes the parameters of all the components of life: the potential, life activity in relation to some objective or subjective standards. In other words, this means how a person evaluates himself, his abilities in society and relationships within the team [*Tkachenko A, 2004*]. The essential components of life quality structure are the conditions and lifestyle of patients and their satisfaction with them. Living conditions imply the environment a person lives in, his level of health, material support, the ability to meet needs in accordance with the cultural and value system he possesses [*Yevsina O, 2003*]. Quality of life is an integral characteristics of a patient's physical,

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functional, social performance, based on his subjective perception. The most important component of life quality is the psychological state [*Novik A, 2007*]. In the past, the main criteria for recovery or remission in a variety of pathologies were the elimination of inflammatory phenomena, removal of tumors, restoration of organ function, expansion of motor activity, etc., whereas currently, along with successful treatment, the degree of a patient's psychological comfort, both inner and within society he resides in, is extremely important. [*Senkevich N, 2000; Furmanov I, 2010*]. Advances in medicine have allowed to pay more and more attention to the life quality of patients with various serious diseases, including those with genetic pathologies, for which there has been no etiotropic and even pathogenetic treatment developed yet. Among these nosological forms there are a number of rare genetic pathologies, accompanied by the formation of ossificates and calcifications of soft tissue mass and followed by disability. Such diseases include fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH). In medical literature they are often described under the term "ossifying myositis" which is outdated today. Both pathologies are classified as rare autosomal dominant diseases manifested by steadily progressing ossification and/or calcification of soft connective tissue mass (muscles, fascia, tendons) accompanied by various congenital bone and/or articular abnormalities [*Kaplan F et al., 2008; Antelava O et al., 2015*].

Different heterozygous mutations of an autosomal dominant nature that arise de novo, as a rule, are the genetic substrate of FOP and POH, but a family inheritance is also possible.

The metaplastic process of ossification and/or calcification develops as a result of disruption of intercellular junctions, disruption of cellular signaling due to a change in the receptor protein caused by gene defects i.e. a heterozygous mutation in the form of substitution of amino acid arginine for histidine at position 206 R (206) H in region 23-24 of chromosome 2 in the ACVR1 gene in FOP and a mutation of the GNAS gene in chromosome 20, including 13 coding exons in POH [*Shore E et al., 2006; Mikhalyova G et al., 2011; Sun H et al., 2019*].

Heterotopic ossification processes are preceded by phases of inflammation, fibroblast proliferation, and marked angioneogenesis.

Pathological processes are usually provoked by mechanical effects (injuries, surgical interventions, etc.), infectious agents (usually viruses). Spontaneous debut and progression of the disease are also possible.

The first manifestations of FOP most often occur in childhood appearing in the form of tumor-like mass in the soft tissues of the neck, head, and back, followed by ossification (Fig. 1). Fever is possible.

Gradually, contractures of joints adjacent to the ossificates and calcinates on the spinal cord develop. This leads to limited mobility in the joints (Fig. 2), the spine, up to the patient's partial or complete inability to perform self-care.

Often, contractures of the temporomandibular joints are formed. Then the patient has difficulties opening his mouth wide, and taking an ordinary meal becomes a problem. Dental pathological processes are resolved with great difficulty, contractures become aggravating as any traumatic effect on the joints potentiates their formation [*Kaplan F et al., 2003*].

Patients with FOP have congenital bone abnormalities, usually represented by short thumbs, synostosis of the fingers, fusion of cervical vertebrae surfaces, costovertebral joints; short neck of the humerus. The main and necessary diagnostic bone sign is congenital deformity of the big toes manifested by shortening or clinodactyly (Fig. 3).

As a rule, there is no laboratory data on inflammatory activity in patients with FOP.

In addition to problems with self-care, children often develop skeletal deformity, their appearance changes, thus aggravating their psychological disorders and becoming an obstacle to successful integration into society (Fig. 4).

In progressive osseous heteroplasia, in contrast to FOP, the spontaneous ossification of connective tissue mass is preceded by calcification, moreover, an obvious trigger factor is often absent.

Sometimes, with age, the progress of the disease slows down, whereas, ossification progresses steadily in FOP patients.

Clinically, the disease often debuts with subfebrile condition, the appearance of painful seals in the dermis, subcutaneous fat, muscle, followed by calcification, and then ossification, stiffness and reduced

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

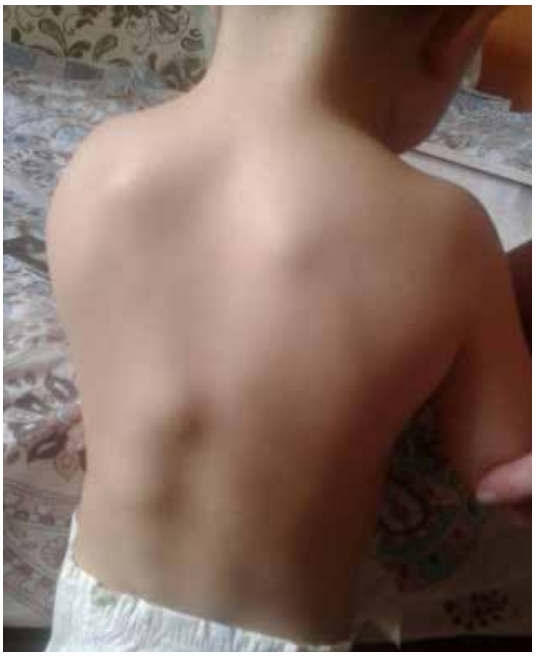

***FIGURE** 1. Ossification on the back of a 1,5-year-old child with FOP.*

***FIGURE**. 2. Limited mobility in the shoulder and elbow joints in a 2.5-year-old child with FOP. He is unable to raise his hands higher. Ability to take the hands down is retained.*

***FIGURE**. 3. Congenital anomaly - deformity of the big toes in a 3-month-old (A), 5-month-old (b), 13-year-old (c) child with FOP.*

range of movements. Bone tissue appears in places where it should not be [*Ringel M et al., 1996; Berezhnoy V et al., 2014*].

It should be mentioned that, in contrast to FOP, irreversible changes of the skin occur in POH and can be manifested by a crimson-cyanotic coloring, fibrosis, and adhesion to subcutaneous fat (Fig. 5). In patients with POF, the skin always remains intact.

Calcification and subsequent ossification also lead to the formation of contractures of adjacent joints (Fig. 6).

In the presence of obvious clinical symptoms, an early and accurate diagnosis is almost always absent due to the rare occurrence of these diseases and the low awareness of pediatricians, orthopedists, oncologists, rheumatologists, that is, specialists who the children with FOP and POH usually encounter first.

Despite the fact that diseases related to "ossifying myositis" have been known for a long time, since the 17th century, when the "ossified patient" was first described, the genetic nature of the pathology was discovered only in 2006 [*Shore E et al., 2006*].

Moreover, the question of the quality of life, the psychological state of these patients, as a rule, receded into the background, since the discussion of the problems of the pathogenesis of the disease, attempts of drug therapy, and the abilities of patients' physical adaptation seemed incomparably more essential to the medical community.

We strongly believe that it is important and interesting to discuss the problem of life quality and the psychological state of such patients.

Under our supervision, there are 33 children with the so-called ossifying myositis, among them

***Figure**. 4. Skeletal deformity, contracture of the right hip joint in a 14-year-old girl with FOP.*

***Figure** 5. Soft tissue calcification in a 5-month-old patient with POH.*

28 children with FOP, and 5 children with POH aged from 5 months to 17 years. No gender differences. All the pictures presented in the article depict the patients we observe.

It can be stated that we are only at the beginning of the path and so far are not ready to offer specific methods of psychological examination, special testing, not even methods of improving the psychological state of these patients. At the initial stage, we would like to at least figure out the range of psychological issues that we have to deal with.

The purpose of this article is:

- √ description of the psychological problems of children with limited mobility related to congenital progressive diseases of genetic origin and their parents; attempts to find solutions to these problems;
- √ an attempt to discuss the problems of correction and prevention of emotional and behavioral changes in such patients;
- √ clarify the issues of psychological assistance to children and their parents as far as possible;
- √ an attempt to reduce the influence of adverse objective factors on the mental state of both children and their parents;
- √ discussion of potential professional orientation of patients in the future.

The debut of the disease is of great psychological importance. An early onset in the first three years of life is considered to be a prognostically unfavorable factor. But the child is getting older and is growing up "with the disease". Psychological, often dramatic discomfort arises as the child enters into society. And here a lot depends on teachers, educators, managing the behavior of peers. According to our experience and with the assessment of parents' behavior, a child can have a non-traumatic integration in the children's community and feel more or less comfortable there due to close interaction with teachers at school and at childcare centres.

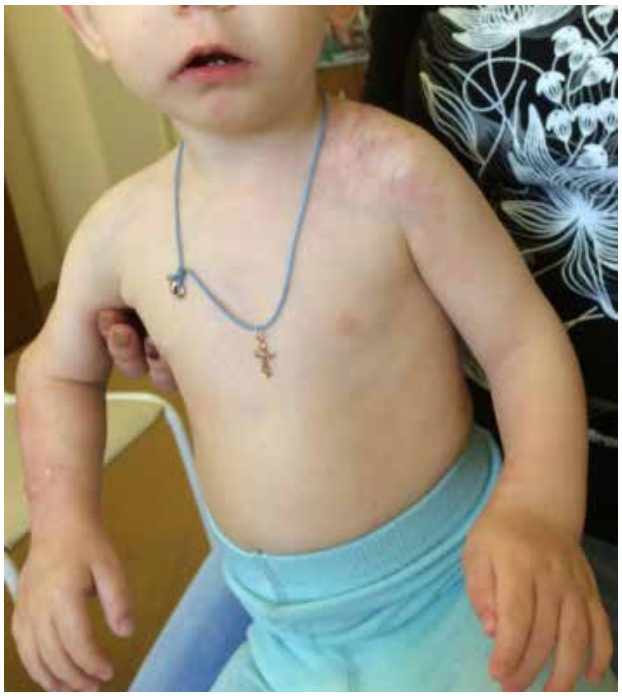

***Figure**. 6. Contractures in the shoulder, elbow, and wrist joints in a 2-year-old child with POH. The maximum range of motion is deomonstrated.*

There might be a completely different situation if a disease is revealed at prepuberty or puberty period, when a patient is shocked to realize the presence of a serious, incurable, progressive disease. A teenager often develops rejection, denial of the disease. It takes time for psychological adaptation, and seeking one's new "self" in the community of peers.

In our practice, such patients and their parents changed doctors, hoping for the mistake of the previous doctor who had diagnosed the disease. As a rule, they overcame a psychological failure on their own within the family. Probably, contact with a professional psychologist would alleviate and accelerate the process of "adaptation to the disease". However, none of our patients sought help of a professional psychologist. It can be assumed that the specific public mentality does not allow to overcome the internal barrier of parents and patients and to request assistance of a professional specialist in these situations. Although psychological consultation has become widely available in modern society.

Suitable choice of profession is of great importance. The patient's limited mobility, often the reduced ability to perform self-care and a cosmetic change in appearance should be taken into account. An important restricting factor is the risk of a potential injury, that may lead to a progression of the disease, causing new ossifications and hence, new contractures.

In our survey, there have been cases when adolescent patients chose the profession of a psychologist and defectologist, i.e. a specialist who works with patients similar to themselves. Their choice was rather spontaneous. We believe that it makes sense to work actively to psychologically prepare such children for an appropriate profession.

The psychological problems of adults and parents are inseparable from the problems of children. The range of questions is wide enough. How to behave with a patient with limited mobility in the presence of another healthy child? Everyone realizes that it is necessary to cultivate empathy and a sense of support. But where does compassion end and degrading pity begin? How to outline boundaries? In addition to the parental "instinct", professional help from psychologists will be useful here.

An extremely difficult question for parents is whether to have another child, if the only one has a genetic pathology. FOP, as a rule, occurs spontaneously. Yes, there are successful cases of prenatal diagnosis. But, what should they to if a congenital pathology is revealed by means of a genetic analysis of the biological material of the fetus (obtained by amniocentesis, chordocentesis)? The mental development of such children does not suffer. Should they terminate the pregnancy? What decision should parents make? The task of the doctor is to inform about the risks. And the choice must be made by the parents themselves. In our practice, we had a case when parents decided on a second child, but the latter was born with a severe form of cerebral palsy.

Probably, we again need the support of a psychologist, help in creating tolerance for risk, motivation to make one choice or another and then not to regret their decision whatever the outcome might be.

While interacting with parents and consulting the children, we faced problems such as underestimation of the severity of the disease by mother and father, although they seemed to be well-informed. For example, they encouraged their daughter's free activities in the pool, which, of course, can have a favorable physical and psychological effect. But at the same time, they demanded a certificate from the doctor for enrolling the child in the professional swimming section. They were not ready to take into account the fact that excessive, imposed physical effort, possible injuries can potentiate the progression of the disease. The same parents insisted on sending the girl to the orthodontist for occlusal restoration with the help of special devices, ignoring the traumatic effects of dental intervention, the risk of temporomandibular joint contractures.

With the increase of information about rare genetic diseases, the free flow of data among the medical community, which of course, is a great benefit, a new unexpected psychological problem has arisen. As an example, we will present two cases of a genetic diagnosis of FOP in children aged three and five months, from different families. The reason for the examination was the changes in the toes, which caught the attention of the orthopedist who was aware of the FOP signs.

Clinical syndromes of FOP were absent, and the information was a shock for the parents. How should a doctor behave? How can he identify the condition of the child? "Diagnosed with FOP?" "Carrier of a pathological gene FOP?" Of course, it is necessary to give the relatives information and recommendations about the correction of lifestyle of an infant for now and for the future. But the psychological problem was not addressed. And these challenges tend to increase with the further improvement of medicine. Therefore, there is a need for psychological consultation of "somatic" specialists, and even additional training on the basics

of psychology in the context of relationships with such patients and their parents.

When consulting families with children with ossifications and/or calcifications, a doctor should establish a psychological limit for himself. Certainly, it is necessary to provide reliable information adapted to the perception of the listeners. But where does the psychological support for patients and parents end and the unreasonable discussion of the illusory prospects of unproven therapy begin? When does the doctor inspire unreasonable hopes? There is no answer to this question yet. These issues require psychological literacy of a doctor who is in contact with severe chronic patients.

A child is always tied to society psychologically, whether directly or indirectly. Even if he is isolated in the family, society inevitably affects his parents and teachers. The psychological state of the child largely depends on the mentality of the society or micro-society. Especially if a child is a "disabled" patient.

The maturity of any society and its adequate psychological response to members with disabling conditions are determined by the ability to create the so-called horizontal connections. That is, to form communities on their own initiative based on interests and common problems and absolutely without any boost or regulation by the state.

An example of creating such an organization is "Living with FOP" Society [http://foprussia.ru/]. The Society unites parents and patients of all ages with ossifying myositis. It opened in Russia quite recently, in 2014. The initiators of the Society were the parents of children with FOP.

Of course, their main activity has a practical orientation. The company regularly organizes scientific conferences dedicated to medical research on the problem of studying pathogenesis, therapy of FOP, inviting foreign experts in this field. The fact that the Society has achieved recognition of fibrodysplasia ossificans progressiva by the state as an orphan disease is a huge success; besides, this disability is now assigned to patients once and for life and the annual re-examination has been canceled [*Kovalenko-Klychkova N et al., 2014*].

However, in the light of the issues discussed, the support provided by the Society and represented by "experienced" patients and their parents to those who have just faced the problem of FOP is invaluable. Among the specialists closely interacting with the members of this society, there are many rheumatologists, orthopedists, geneticists, and pediatricians. But there are no professional psychologists in this organization. We strongly believe that this gap needs to be compensated and psychologists should be included as experts to help patients and their parents, as well as consult the doctors supervising these patients.

Therapeutic methods for FOP and POH have not been developed so far. The information presented in literature has no evidence base due to the rare occurrence of these pathologies.

There are no convincing data on the effectiveness of any therapy, including glucocorticoids, the use of which is supposed to be considered during the acute period [*Rhen T, Cidlowski J, 2005*]. The use of bisphosphonates (pamidronic, zoledronic, alendronic acid) orally remains common in therapeutic practice. The use of muscle relaxants to reduce secondary spastic muscle tension and relieve pain is under consideration [*Glaser D, Kaplan F, 2005*], as well as cromoline, a stabilizer of mast cells, whose role in the pathogenesis of the disease is being discussed [*Gannon F et al., 2001*]. Proinflammatory prostaglandins are powerful molecular co-stimulators of ossification, which allows us think of the possible role of the selective cyclooxygenase-2 inhibitors in the symptomatic treatment of FOP and POH [*Weinreb M et al., 1997*]. However, all these drugs do not allow to achieve any significant results.

Despite the current lack of etiotropic and pathogenetic therapy of FOP and POH, intensive scientific research is underway to find effective drugs that can block the formation of ossificates. Various aspects of application of possible drugs are being sought. A genetic model of FOP has been created in animals, on which samples of drugs are tested [*Grgurević L et al., 2019; Lin H et al., 2019; Wentworth K et al., 2019; Sekimata K et al., 2020*].

On the other hand, the foreign analogues of the domestic "Living with FOP" Society (International Fibrodysplasia Ossificans Progressiva Association) are actively developing and putting into practice the simplest inexpensive devices increasing the range of mobility for patients, helping to dress and eat independently, serve themselves in the toilet, use a bathroom without help. At conferences, various adjustable spoons, brushes, hooks, special canes, etc. are presented.

Unexpectedly, we were faced with the psy-

chological problem of some patients with FOP who were not willing or were embarrassed to use facilitating household appliances. For example, a teenager with FOP, having joint contractures of the lower extremities and secondary arthritis, categorically refused to use a special cane, which would help reduce the load on the joints, alleviate pain, thus slowing down the progression of the disease. We failed to convince him. Probably, the appropriate psychological professional approach would help to achieve success.

FIGURE. *7. A 17-year-old patient with FOP. The face is not hidden at the request of the girl and her parents.*

The old saying that "If you cannot change the situation, you can change the way you think about it" takes on a special meaning with patients with disabling genetic diseases. It is extremely difficult to convey this idea to a disabled child who understands the essence of his progressive illness. As a positive example, we are demonstrating a photograph of our patient, who, together with her parents inspired a number of children in the "Living with FOP" Society with her cheerful attitude to life (Fig. 7). To be honest, it is worth mentioning that the doctors had no contribution in solving her psychological problems.

Thus, we tried to outline the range of psychological problems that parents and their children with genetic ossificates and/or calcification, with limited mobility and deforming cosmetic problems might experience.

In our opinion, it is necessary to raise such problems at medical forums, publish information about them in medical journals, share experience and exchange methods and practices with other specialists (oncologists, hematologists, surgeons, etc.) so as to solve these psychological problems.

We believe it is important to include professional psychologists and psychiatrists in the process of solving these issues, invite them to conferences and forums devoted to these rare genetic problems.

Somatic specialists should be aware of the basics of the psychology of disabled patients and their parents. Psychological consultation of such a contingent should not be spontaneous, without knowledge of objective laws, specific aspects of personality psychology. We should constantly remember that "If a patient cannot be cured, this does not mean that he cannot be helped".

The authors will be grateful for the responses of pediatricians, doctors of narrow specialties (rheumatologists, orthopedists, neurologists, geneticists, etc.), as well as professional psychologists and psychiatrists, to this article.

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