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Parents Facing Their Child's Rare Disease. A Boy with Tatton-Brown-Rahman Syndrome

Rodzice wobec choroby rzadkiej u dziecka. Chłopiec z Tatton Brown Rahman Syndrome

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Abstract

Aim. A rare disease (in the European Union) is defined as a disease occurring no more often than in 5:10,000 people. In most cases, it affects children, which irreversibly affects the functioning of the entire family. The aim of this article is to show the functioning of a child with a very rare genetic syndrome – Tatton-Brown-Rahman Syndrome.

Methods and materials. Through a phenomenological description of the conducted studies on an individual case, the author presents the medical, therapeutic and pedagogical procedures undertaken, as well as the parents' efforts aimed at the child's well-being and comprehensive development.

Results and conclusion. The research results obtained may contribute to increasing awareness of the occurrence of new rare diseases, and encourage the search for not only medical but also therapeutic solutions that support the development of the child and its parents. Taking into account the development of genetic research and the increase in awareness

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of rare diseases, the search for medical and therapeutic solutions is becoming an indispensable element. That is why it is so important to expand knowledge about occurring genetic diseases among therapists and educators in order to consciously conduct therapeutic tasks and support parents in making choices tailored to the needs and capabilities of their children.

Keywords: parents of a child with a rare genetic disorder, Tatton-Brown-Rahman Syndrome, therapeutic treatment, diagnosis procedure, rare disease

Abstrakt

Cel. Choroba rzadka (w krajach Unii Europejskiej) określna jest jako jednostka chorobowa występująca nie częściej niż 5:10.000 osób. W większości przypadków dotyka ona dzieci, co bezpowrotnie wpływa na funkcjonowanie całej rodziny. Celem niniejszego artykułu jest ukazanie funkcjonowania dziecka z bardzo rzadkim Zespołem genetycznym Tatton-Brown-Rahman.

Metody i materiały. Artykuł przedstawia fenomenologiczny opis indywidualnego przypadku dziecka z Zespołem Tatton-Brown-Rahman. Opisuje podjęte postępowanie medyczne, terapeutyczne i pedagogiczne, a także wysiłki rodziców w trosce o dobro dziecka i jego wszechstronny rozwój. Dążenie do uzyskania pełnej diagnozy medycznej, logopedycznej i pedagogicznej. A także zalecenia co do proponowanych form terapeutycznych. Podjęte przez rodziców dziecka decyzje co do postępowania terapeutycznego, poszukiwanie odpowiednich metod i technik, tak by w sposób holistyczny wspierać rozwój dziecka.

Wyniki i wnioski. Uzyskane wyniki badań mogą przyczynić się do wzrostu świadomości odnośnie występowania nowych chorób rzadkich. Zachęcić do poszukiwania rozwiązań nie tylko medycznych ale i terapeutycznych wspierających rozwój dziecka i jego rodziców. Biorąc pod uwagę rozwój badań genetycznych i wzrost świadomości dotyczącej chorób rzadkich poszukiwanie rozwiązań medycznych, jak i terapeutycznych staje się elementem nieodzownym. Dlatego tak ważne jest poszerzanie wiedzy na temat występujących chorób genetycznych wśród terapeutów i pedagogów, tak by świadomie prowadzić zadania terapeutyczne i wspierać rodziców w dokonywaniu wyborów dostosowanych do potrzeb i możliwości ich dzieci.

Słowa kluczowe: rodzice dziecka z rzadką chorobą genetyczną, Syndrom Tatton--Brown-Rahman, rzadkie choroby genetyczne, postępowanie terapeutyczne, postępowanie diagnostyczne

Introduction

"Rare diseases are common" – the statement that Urszula Klajmon-Lech (2018, p. 7) draws attention to has its justification and is not a contradiction in itself. The number of rare diseases known to date is estimated at 8,000–10,000 (Rare diseases, n.d.a). This concerns 350 million people globally (which is 6-8% of the world's population), including about 30 million in the European Union and 2–3 million in Poland (Rare diseases, n.d.a). This data is underestimated, which results mainly from the diagnosis of new diseases (about 50 per year). The vast majority of them, as many as 70%, are revealed before the age of 2 years, and in over 50% of cases they are accompanied by developmental delays, both psychomotor and intellectual, which significantly affect the functioning of the entire family, and above all the child and their parents. These diseases pose medical, social, economic, therapeutic, and pedagogical challenges. As Robert Śmigiel points out, they are one of the most common causes of hospitalisation and the main cause of neonatal and infant mortality" (Śmigiel, 2023, p. 43) (one third of children with rare diseases die before the age of five). Despite their great diversity, they share common features such as:

> […] usually chronic or severe course; often coexist with physical and/or intellectual disability; life expectancy of patients is often shortened in relation to the average life expectancy of the population in which they live; most of them are genetically determined (80%), which is often associated with an increased risk of disease occurrence in other people in the family; diagnosis is often delayed, which results in lack (or delay) of appropriate medical care; the cost of their diagnosis and treatment is usually high; treatment is currently available to a small percentage of patients (5%) (Rare diseases, n.d.a)

Therefore, it is necessary to implement the Rare Disease Plan for 2024–2025, which postulates work in six key areas such as:

> […] establishing Expert Centres for Rare Diseases (Rare Disease Expertise Centre, abbreviated: OECR) and analysing the billing products introduced for them; improving access to diagnostic tests used in the diagnosis and treatment of rare diseases; improving access to medicines and special nutritional products for rare diseases; Polish Register of Rare Diseases (Polish Registry of Rare Diseases, abbreviated: PRCR); Rare Disease Patient Card; running an Information Platform (Rare diseases, n.d.b)

Paying attention to the definitional and statistical approach to rare diseases, one cannot ignore the key element that is striving for the correct diagnosis of the disease. Due to the progress in medical sciences, including in the field of genetics (since 80% of rare diseases have a genetic basis), making the correct diagnosis is increasingly faster and allows for taking the necessary actions covering not only the child but also the entire family by providing genetic counselling regarding, among other things, the risk of the disease recurring in the family. This opens the door to:

> […] benefiting from the therapy for a rare disease, if it has been developed, sometimes therapy with a drug used in other diseases (off label), participation in clinical trials for the development of therapy, appropriate medical care, individually selected (*e.g.*, avoiding specific harmful factors, preventing complications, proper rehabilitation, oncological supervision, *etc.*), implementation of procreation plans (after the diagnosis, parents decide to implement procreation plans 8 times more often), easier acceptance of the disease; support from other families with the same disease (Rare diseases, n.d.b)

In many cases, early diagnosis (in the neonatal-infant period) is of key importance, as it allows for the application of appropriate treatment and thus enables a significant improvement in the patient's quality of life (Śmigiel, 2023). However, in this area, there also occur great obstacles that depend on the state policy, economic possibilities, and access to treatment, which are often a huge barrier. The market potential of drugs for rare diseases is less attractive economically than in the case of common diseases, which is why in 1983 the government of the United States signed an act that significantly influenced research development, possibilities of co-financing for grants, as well as tax relief, supporting the approval of hundreds of orphan drugs in the USA and leading to the introduction of similar regulations in European countries (Lancet Global Health, 2024). The parents' hope for the existence of a drug that can significantly improve the quality of life of their child sometimes turns out to be in vain, because these drugs are very expensive. Therefore, conservative treatment covers 95% of patients, and the remaining 5%, despite being qualified, often have to wait for treatment even several years until the drug reaches the country (Gajda, 2024). For example, Hemgenix, a gene therapy for the treatment of Hemophilia B based on an adeno-associated virus vector, costs US$3.5 million per dose in the US (Gajda, 2024) Therefore, systemic actions are being taken to improve the quality of life of persons living with rare diseases and their families. These include, among others, UN Resolution 76/132 – *Addressing the challenges of persons living with a rare disease and their families* – adopted by the General Assembly on December 16, 2021 (United Nations General Assembly,

2021), presenting postulates to be implemented by 2030, as well as actions taken by the European Union. They assume:

> […] creating and supporting European Reference Networks (ESR); developing a European platform for the registration of rare diseases (EU RD platform) and its management; supporting the development of nomenclature, codification and the register of rare diseases; supporting the labelling and authorization of orphan medicinal products for trading; expanding the knowledge base also through research and innovation; developing new therapies and diagnostic tools for rare diseases; adapting rare disease registries and data to the FAIR concept, so that they are findable, accessible, interoperable and suitable for reuse (so-called *FAIRification*); improving the recognition and visibility of rare diseases, also at global level through the International Rare Disease Research Consortium (IRDiRC); empowering patient organizations; promoting the development of national plans and strategies for rare diseases (European Commission, n.d.).

All postulates give great hope for changing the situation that concerns millions of patients around the world, as well as the quality of life of their families, whose functioning without appropriate, comprehensive support (medical, psychological, educational, economic, etc.) is impossible. Because it is the family that carries on its shoulders the enormous burden of the child's illness, including an illness about which often little is known, and the only treatment that can be offered is symptomatic treatment, as in the case of Tatton-Brown-Rahman Syndrome.

Theoretical Background

Tatton-Brown-Rahman Syndrome (abbreviated: TBRS) is a rare genetic disorder caused by pathogenic variants in the DNMT3A gene. The condition is also called DNMT3A overgrowth syndrome. It was first identified in 13 people in 2014 by K. Tatton-Brown and N. Rahman, who were researching the genetic causes of overgrowth. As of 2022, only 90 cases have been described, which have been analysed in detail by Ostrowski and Tatton-Brown (2022). According to data presented by the Tatton-Brown-Rahman Syndrome Community, 250 cases of people with this genetic disorder have been diagnosed by 2021 (TBRS Community, n.d.), but it is not clear how common this syndrome is. Work is underway to create a database of people with this condition. It is likely that, thanks to the availability of appropriate diagnostics (whole genome sequencing methods), the detectability of this disease will increase.

Individuals with TBRS have subtle but characteristic facial features: a round face with rough features, thick, horizontal, low-set eyebrows, narrow (measured vertically) palpebral fissures, and prominent upper central incisors (facial gestalt is most easily recognized in adolescence), usually tall, increased weight, and a large head circumference ≥2 standard deviations above the mean for age and sex, (also known as macrocephaly) (Ostrowski & Tatton-Brown, 2022). In most reported cases, global developmental abnormalities have been observed, such as: intellectual disability (from mild to severe), speech disorders, tall stature, hypotension, joint hypermobility, epileptic seizures, including various types of febrile seizures, and in some patients an increased risk of developing acute myeloid leukaemia (AML), behavioural/psychiatric problems, kyphoscoliosis, cryptorchidism, circulatory system disease, and respiratory abnormalities. It is worth noting that the syndrome varies in terms of the severity and occurrence of the above-mentioned symptoms.

The basis for diagnosis is the clinical picture (the individual features described above), family history, and the presence of a heterozygous pathogenic variant in DNMT3A identified by molecular genetic testing. Currently, no uniform clinical diagnostic criteria for TBRS have been published. There are two options for approaching the diagnosis of the disease.

Table 1

Diagnosis of Tatton-Brown-Rahman Syndrome

		Single-gene panel	**performing DNMT3A sequence analysis as a first-line test to detect small intragenic deletions/ insertions and missense, nonsense, and splice site variants**
Option 1	When phenotypic results suggest a diagnosis of TBRS	Multigene panel with overgrowth and/or intellectual disability	Includes DNMT3A and other genes of interest to identify the genetic cause of the disease
Option 2	When the phenotype is indistinguishable from many other inherited disorders characterised by intellectual disability, or the clinician is not familiar with the TBRS phenotype,	comprehensive genomic testing that does not require the clinician to determine which gene is likely to be involved	Exome sequencing is most commonly used
			Genome sequencing is also possible

Source. Elaboration based on Ostrowski & Tatton-Brown, 2022.

The two diagnostic options presented above stem largely from the progress in molecular diagnostics. Given the high incidence of genetic diseases, as well as the highly

diversified phenotypes in individual diseases, genetic tests that allow for whole exome sequencing (WES) provide a faster diagnosis without the need to select a candidate gene for targeted molecular analyses (as in the case of single-gene sequencing using the Sanger method or NGS (next generation sequencing) technology) (Chwiałkowska *et al.*, 2023). This is also visible in the summary of molecular genetic tests used in diagnostics of the TBRS Syndrome presented by Philip J. Ostrowski and Katrine Tatton-Brown, where detection of disorders in the DNMT3A gene is identified in >90% by sequence analysis, and in <10% by gene-targeted deletion/duplication analysis (Ostrowski & Tatton-Brown, 2022).

The mode of inheritance of a genetic disorder is very important for the entire family. Very often, the child's parents blame themselves for passing on the disease to their offspring. In the case of TBRS Syndrome, disorders most often occur as a result of the occurrence of a pathogenic *de novo* variant in the DNMT3A gene. This means mutations in the genetic material leading to the development of a genetic disease that is not inherited from the parents, but arising during the child's conception, cell division and embryo development. This is a situation in which the child is affected by a genetic disease, even though neither parent passed on the mutated gene. Therefore, in such a situation, the risk of the disorder in the proband's siblings is low (slightly higher than the population risk, due to the inability to exclude germline mosaicism). On the other hand, each child of a person with TBRS Syndrome has a 50% chance of inheriting a pathogenic variant of the DNMT3A gene.

Treatment of the discussed syndrome is based on an individual and holistic approach to the patient. It is symptomatic treatment, which, due to the diverse phenotypes of the disease, is adjusted to the needs. Currently,

> […] there are no published clinical practice guidelines for Tatton-Brown-Rahman syndrome (TBRS). Since most people with TBRS are in good general health, a pragmatic approach to treatment is recommended. It should consist of a series of initial assessments at the time of diagnosis, education of the patient/family about potential complications, and regular review of symptoms with treatment adjusted to the patient's needs (Ostrowski & Tatton-Brown, 2022, https://www.ncbi.nlm.nih.gov/books/NBK581652/)

To deepen the diagnosis, the following are recommended: physiognomy assessment, developmental assessment, neurobehavioral assessment, neurological follow-up, orthopaedic and rehabilitation consultation, echocardiogram, polysomnography, cryptorchidism testing in males, haematological care, and genetic counselling. From this outlined description of the disease, there emerge a number of challenges emerge that are faced by the parents of a child with TBRS, as well as the child themselves.

The diagnosis itself is usually the stimulus that initiates taking action to improve the quality of life of the child and the functioning of their family. This is particularly evident in case descriptions, which are a valuable research source that brings the story of the child and their parents closer, and also gives a picture of the diversity and individual character of the disorder.

Methodology

In the case of rare diseases, each person who has a given disorder is a valuable source of information that can contribute to improving the quality of life of people with that given disease. Therefore, it is so important to make case studies that take into account not only the medical approach, but also provide an interdisciplinary view of the individual with a given deficit.

Qualitative research conducted from February to June 2024 provides a description of the functioning of the child and his parents struggling with the diagnosis received, and consequently the actions they took to ensure the child's development would be as harmonious as possible. The research included an interview in the form of a conversation with the child's parents, an interview in the form of a conversation with the speech therapist conducting classes with the boy, observations of the child during music therapy classes, and an analysis of the diagnostic documents received.

The boy was born in March 2020 after a normal pregnancy. He is the first child in the family. After birth, the child did not have any developmental defects, but the parents' attention was drawn to movement problems and delayed speech development. He underwent surgery due to bilateral cryptorchidism, as well as eye surgery. His global development was disharmonious. The parents undertook genetic testing of the child when he turned 3. At that time, the boy already showed a significant delay in psychomotor, speech and intellectual development. The diagnosis from the rare diseases centre shows that:

> […] in a physical examination at the age of 2, the boy's body weight reached 13 kg, OFC 47 cm, there were facial dysmorphic suggestive of MPS, but not as numerous pathogens. Psychomotor development is delayed; he does not speak, and he is hyperactive. Motor development is normal; he has been walking since the age of twelve months. The testicles are wandering. Hyperactivity, strabismus are observed. The boy looks into the eyes, is nicely embarrassed, and follows instructions. In a physical examination at the age of 2.5, the body weight is 15 kg, height 98 cm, OFC 48 cm. The child plays logically but shows hyperactivity, communicates with parents, and begins to combine words into sentences, but

> parents have a problem understanding the child's needs. Parents notice hyperactivity, balance disorders. In addition, motor clumsiness is observed. In a physical examination at the age of 3, the child is larger than his peers, body weight 17 kg, height 104 cm. Dysmorphic features, hyperactivity, and autistic features are present. (Diagnostic-Therapeutic Centre of Rare Diseases, 2023).

The genetic diagnostic tests performed showed that the child had a normal male karyotype. Due to the suspicion of a monogenic disease, a molecular NGS test was performed in the version with whole-exome sequencing WES and in the TRIO system (proband, mother, father). It showed a heterozygous variant c.541C>T (p.Arg181Cys) in the DNMT3A gene. This variant was excluded in the father and mother; therefore, the sporadic origin of the change (*de novo*) was confirmed. The child was also detected with a heterozygous variant c.1706G>A (p.Trp569ter) in the IRF2BPL gene, which is associated with a severe developmental neurological disorder with developmental regression from the second to tenth year of life and progressive brain changes, impaired body movement (ataxia, dystonia, choreoathetosis), loss of speech and seizures. The identified variant has not been described in the literature but is a molecularly strong variant introducing a STOP codon nonsense variant, the loss of sense. Therefore, it is difficult to understand the potential presence of two severe neurodevelopmental diseases and their impact on the health of the child who currently has a large developmental potential and appropriate social development. After a thorough evaluation of both variants, it is suggested that the latter of the two may not have pathogenic significance for the boy's phenotype. However, it cannot be ruled out that both variants are pathogenic and overlap in terms of clinical symptoms. Therefore, developmental observation is required. In addition, the boy and his father were shown to be carriers of a molecularly strong variant in the RYR1 gene, which, according to the researchers, does not affect the child's phenotype, but it cannot be ruled out in relation to the health of the child and his father (occurrence of malignant hyperthermia) (Diagnostic-Therapeutic Centre of Rare Diseases, 2023).

The recommendations received indicate that the boy requires increased paediatric and multi-specialist care. The child should undergo standard preventive vaccinations. Further increased neurological, oncological-haematological, rehabilitation and psychological care, as well as neurological speech therapy, is necessary. Sensory integration therapy is also recommended. Periodic check-ups at a genetic clinic are necessary. Before planned procedures under general anaesthesia, it is advisable to inform anaesthesiologists about the risk of malignant hyperthermia.

The assessment of the development of sensory integration processes and speech development shows that

> […] the boy has sensory modulation disorders of a vestibular under-reactivity nature, features of tactile defensiveness, and simultaneous proprioceptive under-reactivity. The child also shows certain features of sensory disorders based on movement and postural disorders. It can also be assumed with great probability that the boy also has problems with the proper development of auditory reactions. The boy's visual and auditory attention are significantly reduced, as well as the skills expected developmentally in each of the child's spheres of functioning. The patient presents delayed speech development, which is strongly correlated with improperly functioning sensory integration processes with the vestibular-auditory system (Assessment of the Development of Processes of Sensory and Speech Integration, 2022).

It is worth noting that based on the observation, as well as on the interview with parents conducted as part of music therapy classes in April 2024, the child did not show any signs of auditory hypersensitivity, but rather curiosity and a desire for auditory stimulation, as well as a lack of tactile defensiveness, but rather a desire to stimulate the jaw area, cheeks or lips by pressing objects available in the environment against them, as well as a desire for stimulation through chewing. Currently, the child is under the care of many specialists, and the parents are struggling with choosing the right forms of therapy for their son that would bring measurable results.

Results

For the parents of a child struggling with the described disorders, receiving a diagnosis is, on the one hand, confirmation of what has been observed, and on the other hand, it contributes largely to taking action to ensure the best possible development for their child. This is an inseparable element accompanying parents of children with disabilities.

> In other diseases, such as Down's Syndrome, it is known what to do. What forms of therapy to choose, and how to proceed. In the case of my son, I don't know, we are looking, trying to ensure his best possible development, but whether it will do any good will become clear in a few years. Whether our decisions were right, whether we did the right thing? But we know that without therapy, without rehabilitation, it would be very bad. We see the effects. And we know we will keep doing this throughout our lives, all the time. If we stop, there may be a huge regression. That is why we are trying to act. (The child's father statement shared in an interview in April 2024).

The words spoken by the boy's father show the determination that inseparably accompanies the child's parents. They try to provide the child with access to therapies that, on the one hand, are recommended by doctors, and on the other hand, bring joy to the child who participates in them willingly, such as hippotherapy or music therapy, and also contribute to improving the child's functioning and quality of life. It is also worth paying attention to the amount of therapy and the schedule, which is filled with various forms of support for the child's development, which can be quite tiring for such a young organism.

> My son attends a therapeutic kindergarten, where he has various rehabilitation classes, in addition to rehabilitation, sensory integration classes, hippotherapy, psychotherapy, speech therapy, electrostimulation and music therapy. I know that there is a lot of it, but what to give up? What to do? We try our best. In between all this, there are also doctors' appointments. And time for ourselves. As parents, we also need to take a breath sometimes, spend time just the two of us. To pursue our passions, dreams (The child's mother statement shared in an interview in April 2024).

Therefore, finding the golden mean is an art in itself, providing the child with medical and therapeutic support, while at the same time giving time to rest, regenerate, or play with the parents. For the boy's care takers, the key element, apart from the child's functioning in the motor area or striving for independence in basic activities, is communication. Therefore, the emphasis is placed on speech therapy, electrostimulation, and music therapy, paying attention to non-verbal as well as verbal communication. It should also be brought to attention that all of the therapies listed have their own goals, programs, and structures, which together create the therapeutic process. The effects are, of course, noticeable, but they proceed in small steps.

> The more you can achieve in this first period, the better. You have to strive to maintain the child's level of functioning, because genetic diseases often progress. These changes occur mainly during puberty, which is why appropriate therapeutic treatment in early childhood and its continuation are so important. The boy managed to achieve and develop a lot. This is due to aware parents, therapists and doctors. All of these factors affect the child. That is why cooperation between specialists and parents is so important. Thanks to it, you can achieve more and make the therapies take a proper course (The speech-therapist's statement shared in an interview in June 2024).

Conclusion

The functioning of the family of a child with a rare genetic disease is influenced by countless factors. It depends on the speed of detection of the disorder, the possibility of support from the state, the guarantee of medical, psychological, therapeutic and pedagogical care. With the above-mentioned postulates, assurances and plans, we would like to say: I am checking. Because the number of families struggling with rare diseases in children is growing, and the detection of genetic diseases is increasing. That is why time is so important in this case. It is a keyword that directly affects the life and functioning of many families. The second issue worth mentioning is *knowledge*. More and more information about rare diseases appears in scientific articles, books and on social forums. The exchange of information on the procedure, obtaining help, and searching for appropriate forms of therapy is very important for parents, as well as doctors or therapists themselves. Therefore, each described case contributes to the transfer of knowledge and, consequently, can help others choose treatment methods and techniques and draw attention to a problem that may have been overlooked. Conducting research, collecting information, sharing it, following the stories of patients seems to be key in striving to develop effective methods of action. Concluding, we can say that this is only the beginning. We are waiting for action to be taken and we are trying to take it too. Let's not remain passive. Because knowledge about rare diseases should be shared. Thanks to it, we can contribute to ensuring a better quality of life for our patients and their families.

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