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CHALLENGES OF CARING FOR A PATIENT WITH A RARE DISEASE – AS DEMONSTRATED BY CORNELIA DE LANGE SYNDROME

PROBLEMY OPIEKI NAD PACJENTEM Z CHOROBĄ RZADKĄ NA PRZYKŁADZIE ZESPOŁU CORNELII DE LANGE

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Abstract

There are over 12 500 diseases defined by European researchers as rare disorders occurring in less than 1:2000 live births. The majority of these manifest in childhood. The clinical picture of a rare disorder is dominated by intellectual disability of various severity and organ defects. Targeted therapy is not available for the majority of rare disorders, therefore multidisciplinary patient care is the only means of improving the quality and duration of the patient's life. In this paper, the authors share their experience organizing a system of care for patients with Cornelia de Lange Syndrome. Over the last 13 years, multidisciplinary diagnostics and consultations were provided to 92 patients and their families, including rehabilitation and psychological support. The model suggested here demonstrates a shorter diagnostic process, continuous contact with the patient, his/her family and pediatrician. Guidelines and recommendations regarding the particular rare disease should be published.

Key words: rare diseases, de Lange Syndrome, patient care

Streszczenie

Zgodnie z europejską definicją choroby rzadkie, których zdefiniowano ponad 12 500 występują z częstością poniżej 1:2000 żywych urodzeń. Większość z nich ujawnia się w okresie dzieciństwa. W obrazie klinicznym choroby rzadkiej dominuje różnego stopnia niepełnosprawność intelektualna oraz wady narządowe. Ponieważ w większości nieznana jest celowana terapia, tylko multidyscyplinarna opieka nad pacjentem pozwala na wydłużenie oraz lepszą jakość życia. Autorzy dzielą się swoim doświadczeniem w organizacji systemu opieki nad rzadką chorobą genetyczną – zespołem Cornelii de Lange. W trakcie ostatnich 13 lat objęto opieką 92 pacjentów oraz ich rodziny, proponując wielodyscyplinarne badania i konsultacje. Uwzględniano także rehabilitację oraz pomoc psychologiczną dla pacjentów oraz ich rodzin. Zaproponowany model zakłada skrócenie procesu diagnostycznego, pozostawanie w stałym kontakcie z pacjentem oraz jego rodziną oraz lekarzem pediatrą prowadzącym pacjenta w miejscu zamieszkania. Konieczne jest wydawanie przewodników bądź rekomendacji dotyczących danej rzadkiej choroby.

Słowa kluczowe: choroby rzadkie, zespół Cornelii de Lange, opieka multidyscyplinarna

INTRODUCTION

In recent years we have been witnessing a true revolution in the cytogenetic and molecular diagnostics of rare genetic diseases [1]. Over 12 500 rare diseases (RDs) are currently identified (OMIM and Orphanet databases). About 80% of these have an identified genetic basis. In 75% of RDs the first symptoms manifest themselves in childhood and the typical clinical picture consists of multiple organ defects accompanied by intellectual disability. Effective targeted therapy in this cohort continues to be elusive. Therefore, the treatment goals are to improve the quality and duration of the patient's life [2, 3]. The unique clinical picture of each rare disease demands the use of individualized diagnostic and treatment methods. An experienced patient care team is of utmost importance, because it directly correlates with competence in patient assessment and the care provided. Patients with RDs require multidisciplinary cooperation of doctors, psychologists, physical and rehabilitation medicine specialists, as well as social services.

The Cornelia de Lange Syndrome (CdLS) is a model example of a RD (occurs in 1:10 000-1:30 000 of live births) with a complex clinical picture. It presents with pre- and post-natal microsomy with proportional microcephaly and characteristic facial dysmorphism, frequent defects of the heart, limbs and genito-urinary tract. A large percent of patients experience visual disturbances, hearing loss or deafness, anatomic and functional disturbances of the gastrointestinal tract, intellectual disabilities with little or no speech development and behavioral problems, including autistic behaviors. CdLS cases are subdivided into mild and classical phenotypes [4-6]. In about 60% of the cases the etiopathogenesis is related to point mutations or deletions of the *NIPBL* gene. While in 10% of cases the mutations of the *SMC1, CMC3,RAD21, HDAC8* genes coding for the cohesin protein have been identified as responsible [7-9], in the remaining 30% of patients the etiology remains unknown.

Since 2002 a team of doctors from the Medical University of Gdańsk and the Copernicus Hospital (at the time Wojewódzki Szpital Specjalistyczny im. Mikołaja Kopernika) has been cooperating with the CdLS Association – Poland. By providing care for 92 patients and their families, the team was able to clinically and genetically confirm the diagnoses, as well as to build a system of multidisciplinary diagnostics, treatment and follow-up. The families are in continuous telephone and email contact with the center in Gdańsk and attend the annual meeting in Żnin, where they have additional consultations and follow-up. In addition, a social media page is used to exchange information.

This paper describes the experience of a patient care team working with patients with this RD. It is not an exhausting compilation of knowledge about CdLS but a summary of observations from the practical point of view. We suggest that the challenges we faced while working with our patients and their families are quite typical for many RDs.

Verifying the diagnosis

The clinical diagnosis of CdLS was verified during each hospitalization. In equivocal cases, we consulted the specialists from the Scientific Advisory Council (SAC) of the CdLS – World federation. In 10 cases the diagnosis was revised to: microdeletion syndromes, Smith-Lemli-Opitz syndrome, congenital pituitary insufficiency and Fetal Alcohol Syndrome (FAS). This last diagnosis was suggested particularly carefully because two of our patients had coexisting FAS and CdLS.

Planning the diagnostics

All the patients were invited for a brief planned admission to the Department of Paediatrics, Haemathology & Oncology in the Medical University of Gdańsk. This allowed us to shorten the diagnostic process by scheduling many tests and specialist consultations in a short period of time (maximum 3 days). In addition, the specialists were able to discuss the cases and plan the multidisciplinary follow-up care. All the patients were consulted by a pediatrician, gastroenterologist, neurologist, otorhinolaryngologist, cardiologist, ophthalmologist, physical and rehabilitation medicine doctor and psychologist. If needed, the patients were consulted by an orthopedic surgeon, while the older patients were all seen by an endocrinologist. At this stage some of the patients were enrolled for detailed tests of the gastrointestinal system and anti-reflux procedures.

Fundamental issues – gastrointestinal disturbances and microsomy

Our team's experience demonstrates that the anatomic and functional disturbances of the gastrointestinal tract are the most significant problem for patients with CdLS.

This observation is consistent with the literature, where these disturbances are present in over 70% of the CdLS patients, often with non-characteristic symptoms (infection-prone, self-aggression) [10]. In some cases we initiated anti-reflux therapy and observed improvement despite the lack of unequivocal diagnosis (e.g. due to lack of parental consent for gastroscopy). It is noteworthy that Barett's esophagus was diagnosed in two of our patients.

A major treatment challenge is the lack of increase in normal body mass, despite the use of naso-gastric tubes or gastrostomy. One of the challenges of on-going patient care is to convince the parents that microsomy is typical for CdLS patients. The use of CdLS-specific growth charts devised by Kline et al is helpful [11]. Unwillingness to eat is also quite common, however we noticed that adding spices to food might improve the patient's appetite.

We observed five sudden deaths due to gastrointestinal complications (sepsis, acute ileus). It is important to remember that CdLS patients have a subjectively higher pain threshold, which often delays the correct diagnosis of an urgent complaint. This is also true for patients with other RDs, particularly Prader-Willi Syndrome. Therefore, we warn our patients' families and doctors that each gastrointestinal infection or an episode of distress should be a warning sign and suggest the possible need for hospital admission. We often intervened in case of hospitalization of our patients at regional hospitals.

Organ defects and neurological disturbances

Although heart defects are diagnosed in about 30% of the children with CdLS, they rarely require surgical

intervention. However, regular follow-up by a cardiologist is recommended [12]. Urinary tract abnormalities are noted in 20% of the patients, therefore an ultrasound examination is necessary, with a nephrology consultation if needed [13]. Nearly 100% of the boys with CdLS have cryptorchidism that requires surgical correction. Slight increase in muscle tone was observed in over ½ of the patients, though it usually has no impact on the locomotor function. According to the literature, seizures confirmed by abnormal electroencephalography are diagnosed in 23-26% of the CdLS patients. However, our observations suggest an even less frequent occurence of seizure disorders (18%) and a good response to monotherapy with valproic acid or carbamazepine [14].

Anesthesiological challenges

Gastrointestinal testing, such as gastroscopy, and surgical interventions required the care of experienced anesthesiologists due to the peculiarities of the CdLS patients' cranio-facial anatomy, their non-specific drug reactions (e.g. to benzodiazepines) and the need for individual dosing. Inserting intravenous access and a gastric tubes often requires inhalational induction, despite the obstruction by saliva and gastric contents. The literature suggests avoiding intubation and leaving it as the last resort [15].

Rehabilitation – prothetics, hearing aids, eyeglasses

There is no single and ideal physical therapy system that can be recommended. However, it must be noted that most of the children with CdLS do achieve the ability to walk, although speech therapy is a much more significant challenge. Children with the classical phenotype are not capable of even minimal speech. We observed that the severity of hearing loss did not have a direct correlation with speech development – children with the classical phenotype and normal hearing failed to learn to vocalize syllables. In CdLS motor development often precedes communication development [9, 16]. That is why it is necessary to use non-verbal communication (especially a system of gestures). Although around 30% of the children with CdLS have defects of the limbs, it is commonly known that prostheses are not beneficial and the patients do not tolerate wearing them [9]. We observed similar difficulties with hearing aids, despite the fact that hearing loss or deafness affects 30-40% of the patients. On the other hand eyeglasses are relatively well-tolerated by CdLS patients.

Behavioral disturbances

Aggression, self-aggression and autistic behaviors are typical for CdLS and occur in more than 50% of this patient group [17-21]. These behaviors tend to increase during puberty and in girls reach a peak during pre-menstrual days. Our observations suggest a transient progression of behavioral disturbances in CdLS women aged 21-25 years old, though the cause is unknown. A mother of one of our patients defended her Master's thesis on aggression and self-aggression among CdLS patients and suggested untreated gastro-esophageal reflux and verbal communication disorders as likely causes [22]. As in other RDs, CdLS presents with insomnia and waking up at night without disturbing the day/night rhythm [23]. The use of insomnia medication and sedatives did not prove effective, however melatonin is promising, as it improved the sleep quality of several of our patients.

Cooperation with other centers

We would like to draw attention to the excellent cooperation with some European and American genetic laboratories. The majority of molecular investigations were performed at the Department of Biology and Genetics, Medical University of Gdańsk (Prof. Janusz Limon), at the Department of Molecular and Human Genetics Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA (Prof. J Lupsky) , Grupo de Genetica Clinica, Facultad de Medicine, Universidad de Zaragoza Spain (Prof J. Pié, Prof. F. Ramos) and Sektion für Funktionelle Genetik am Institut für Humangenetik, Universität zu Lübeck,Germany (Prof F.Kaiser). The effects of this cooperation were numerous, repeatedly cited publications. In addition to the very good cooperation with the Department of Pediatric Surgery and Urology for Children and Adolescents at the Medical University of Gdańsk, our best experience in the sphere of cooperation with other centers has been with the World Hearing and Speech Center in Kajetany. Our patients require multiple tympanostomies, therefore they are frequently admitted there and the families bring positive feedback. Another excellent example of cooperation is that with the Surgery Clinic at the 10th Clinical Military Hospital and Policlinic in Bydgoszcz (Prof. Robert Szyca), where our adult patients with gastroenterological disturbances were operated. We have ongoing support of the Children's Memorial Health Institute and the Institute of Mother and Child (both in Warszawa).

Over the years we have built a network of contacts with neonatology wards throughout Poland. Together with the website of the Polish Registry of Congenital Malformations, this helps us to connect with new patients and share the information about the syndrome between neonatologists and pediatricians.

Follow-up with pediatricians

The innumerable amount of telephone and email consultations we provided in the years 2002-2015 assure us that a so-called reference center is a necessary part of the on-going care for a patient with a RD. The questions from pediatricians usually concern the indications or contraindications to vaccinations, issues with feeding, reactions to common illnesses, such as diarrhea or respiratory tract infections. We do our best to share our recommendations with the patient's pediatrician [24].

Challenges

The patient care system we built and maintain allows us to observe the management of patients with RDs in Poland. Patient care is not coordinated, therefore our patients attend numerous separate clinics, which

is time-consuming for the patients and their parents. Many hospitals have financial restrictions, therefore they limit multidisciplinary diagnostics and focus on the patient's single specific reason for admission. A praise-worthy exception in this picture are the neonatology wards which are subject to different budget/billing criteria.

Care for adults with CdLS remains to be organized. Our adult patients are usually microsomic, therefore it is not possible to care for them using equipment that is designed for the average adult and the dosage of medications often confuses doctors from outside the pediatric specialties. Therefore, we suggest that adult CdLS patients should be treated at the existing pediatric wards and outpatient clinics. However, this requires submitting special requests at these hospitals.

CONCLUSIONS

The model of multidisciplinary long-term care for a patient with a RD that we describe here has so far been successful. Based on our experience and the available literature, we drafted recommendations for patients with CdLS and made them available during consultations in Gdańsk and on the website of the CdLS Society – Poland. Our next step is to design a passport for our patients as a way to quickly and reliably convey information about the patient in case of an emergency (e.g. to the emergency responders or the emergency department staff). Cooperation with the CdLS Society and participation in International CdLS Conferences allow direct contact with the families and an exchange of experience, both of which are priceless.

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