Pielęgniarstwo Neurologiczne i Neurochirurgiczne
THE JOURNAL OF NEUROLOGICAL AND NEUROSURGICAL NURSING
eISSN 2299-0321 ISSN 2084-8021 www.jnnn.pl **Case Report**

DOI: 10.15225/PNN.2019.8.2.5

Neurodevelopmental Stimulation of a Child with a Noonan Syndrome with a Non-Frequent Mutation in RAF1 Gene — Case Report

Stymulacja neurorozwojowa dziecka z zespołem Noonana z rzadką mutacją w genie RAF1 — opis przypadku

Teresa Kaczan[1], **Robert Śmigiel**[2], **Magdalena Kazimierska-Zając**[1], **Robert Dymarek**[1], **Joanna Rosińczuk**[1]

[1]Department of Nervous System Diseases, Faculty of Health Sciences, Wrocław Medical University, Poland
[2]Department of Propaedeutics of Paediatrics Rare Disorders, Faculty of Health Sciences, Wrocław Medical University, Poland

Abstract

Introduction. Noonan syndrome (NS) is a genetically determined disease, inherited from autosomal dominant. About 50% of patients have a mutation in the PTPN11 gene, and mutations in the other genes are much less frequent, up to 10–15% for SOS1, RAF1, and RIT1, as well as up to 1–2% for others.
Aim. To present the clinical picture of a child with NS with a non-frequent mutation in the RAF1 gene and to describe a proposal of good practice based on the multi-specialty child care procedures used from birth to 3 years of age.
Case Report. The paper presents a boy with NS and his psychomotor and linguistic development during the 36 months of his life. The infant was born by cesarean section in average general condition and with features of macrosomia. Castillo-Morales rehabilitation techniques were used to improve the coordination of suction, swallowing and breathing. Bobath Neurodevelopmental Treatment was also used on the hospital ward. The NS child's development was assessed using the Munich Functional Developmental Diagnostics (MFDD). At the age of 36 months, the boy presents psychomotor development appropriate for the age of a healthy child. He remains under multidisciplinary team care and is intensively rehabilitated accordingly to both movement and linguistic functions.
Discussion. Management of NS should be comprehensive and multidisciplinary, and continuous monitoring of patients is crucial. Although a number of patients experience learning difficulties and a mild form of mental impairment, the diagnosis of NS does not predispose to mental disorders.
Conclusions. NS is a multi-symptomatic disease that manifests itself in the expression of clinical symptoms requiring the interdisciplinary cooperation of many specialists. The fact is that the identified mutation in the RAF1 gene in patients with NS does not mean they are predestined to develop psychomotor disorders. **(JNNN 2019;8(2):78–85)**
Key Words: Noonan syndrome, RAF1 gene mutation, pediatric clinical diagnosis, interdisciplinary rehabilitation, psychomotor development, interventional speech therapy

Streszczenie

Wstęp. Zespół Noonana (NS) to choroba uwarunkowana genetycznie, dziedziczona w sposób autosomalnie dominujący. Około 50% pacjentów posiada mutację w genie PTPN11. Mutacje w innych genach są znacznie rzadsze, do 10–15% dla SOS1, RAF1 i RIT1, a także do 1–2% dla innych.
Cel. Przedstawienie obrazu klinicznego dziecka z NS z nieczęstą mutacją w genie RAF1 i opisanie propozycji dobrej praktyki opartej na wielospecjalistycznych procedurach opieki nad dzieckiem stosowanych od urodzenia do 3 roku życia.
Opis przypadku. Artykuł przedstawia chłopca z NS, jego rozwój psychomotoryczny i językowy w ciągu 36 miesięcy życia. Niemowlę urodziło się przez cięcie cesarskie w średnim stanie ogólnym z cechami makrosomii. Techniki rehabilitacji Castillo-Moralesa zastosowano w celu poprawy koordynacji ssania, połykania i oddychania. Na oddziale szpitalnym zastosowano również terapię neurorozwojową Bobath. Rozwój dziecka NS oceniono za pomocą Monachijskiej Funkcjonalnej Diagnostyki Rozwojowej (MFDD). W wieku 36 miesięcy chłopiec przedstawia rozwój psychoruchowy

odpowiedni do wieku zdrowego dziecka. Pozostaje pod opieką zespołu wielodyscyplinarnego i jest intensywnie rehabilitowany zarówno pod kątem rozwoju ruchowego jak i językowego.
Dyskusja. Zarządzanie NS powinno być kompleksowe i wielodyscyplinarne, a ciągłe monitorowanie pacjentów ma kluczowe znaczenie. Chociaż wielu pacjentów doświadcza trudności w uczeniu się i łagodnej postaci upośledzenia umysłowego, diagnoza NS nie predysponuje do zaburzeń psychicznych.
Wnioski. NS jest chorobą wieloobjawową, manifestującą się objawami klinicznymi wymagającymi interdyscyplinarnej współpracy wielu specjalistów. Faktem jest, że zidentyfikowanie mutacji genu RAF1 u pacjentów z NS nie oznacza, że są oni predysponowani do rozwoju zaburzeń psychoruchowych. **(PNN 2019;8(2):78–85)**
Słowa kluczowe: Zespół Noonana, Mutacja genu RAF1, pediatryczna diagnoza kliniczna, interdyscyplinarna rehabilitacja, rozwój psychoruchowy, interwencja logopedyczna

Introduction

Noonan Syndrome (NS) is a heterogeneous disease that is genetically determined in terms of the expression of clinical symptoms and of dysmorphic features. The prevalence of this syndrome is estimated to range from 1 in 1000 to 1 in 2500 live births [1].

The main clinical features of the syndrome include cardiovascular (most often pulmonary artery stenosis, intraventricular septal defect, but also hypertrophic cardiomyopathy), lymphatic, musculoskeletal, urogenital, hematopoietic, and nervous system abnormalities [2]. In addition, NS is characterized by facial dysmorphic features (e.g. hyperthyroidism, palpebral fissure pointing obliquely downwards, ptosis, blue or cyan iris, nose with wide and sunken base and extended tip, low attached ear auricle with a thick labrum, moreover, and a short and wide neck with excess skin or webbed neck and a low neckline) [3–5].

The genetic basis of the disease is the presence of a mutation in one of the genes coding proteins that are elements of the RAS/MAPK cell signaling pathway, in which signaling is mediated by mitogen-activated protein kinases (MAPKs) [6–8]. NS occurs as a result of the mutation of one of the 12 known genes: PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1, SOS2, RRAS, SHOC2, and CBL. About 50% of patients have a mutation in the PTPN11 gene, and mutations in other genes are much less common (up to 10–15% for SOS1, RAF1, and RIT1, 1–2% for others [9,10].

The etiology of the syndrome, however, is not fully understood, as in some cases mutations are not identified in the aforementioned genes [2,11]. Although there has been tremendous progress in understanding NS over the past few years, there are still many unexplained issues, including the correlation between genotype and clinical expression. Thus the diagnosis of NS remains difficult and long periods of observations are sometimes required.

The aim of this paper is to present the clinical picture of a child with NS with a non-frequent mutation in the RAF1 gene and to describe a proposal of good practice based on the multi-specialty child care procedures used from birth to 3 years of age.

Case Report

The boy was born at 37 weeks of gestation, complicated by respiratory and vaginal infections, weighing 4090 g. In the fetal ultrasound in the prenatal period, a polyhydramination was suspected. The karyotype of amniocytes collected by amniocentesis was normal. The infant was born by cesarean section in average general condition, with an APGAR score of 4 and with features of macrosomia. Birth asphyxia of average grade was identified. The baby needed respiratory support. Physical examination revealed a short chest, prominent stomach, large head circumference, short upper and lower limbs, an extra finger on the right-hand pedicle, a lobule, low situated earlobes, and an excess of skin on the neck.

The new-born was transferred in a transport incubator to the Neonatal Intensive Care Unit (NICU). In the ward, the child was placed in an incubator, and biphasic nasal continuous positive airway pressure (BP-NCPAP) was continued; umbilical cord blood was collected, and an antibiotic was given. A chest X-ray was performed, revealing grade III Respiratory Distress Syndrome (RDS). After premedication, the new-born was intubated and a respirator was attached to provide Synchronous Intermittent Mandatory Ventilation (SIMV). The initial stable condition of the child was followed by rapid deterioration, desaturation, and heart failure.

On subsequent days the baby's condition became severe, mechanical ventilation continued, and antibiotic therapy, diuretics, as well as an infusion of catecholamines were administered. The baby was fed parenterally and trophic nutrition was started. Copious secretions were observed in the upper and lower respiratory tract. Several repeated bacteriological studies of bronchial secretions were negative. Attempts to extubate the child failed. Two systemic steroids were administered, and due to increased infectious expression, antibiotic therapy was modified.

Ultimately, the child was extubated at 28 days of age but still required non-invasive support with BP-NCPAP for 4 days, followed by passive oxygen therapy and inhalation. Due to anemia, epoetin-beta and hematopoietic drugs were administered. The consultant cardiologist reported hypertrophy of the

ventricular septal defect and Eustachian valve, as well as a small amount of liquid in the left pleural cavity. Diuretics were administered and rehabilitation was performed.

The heart was monitored several times by Holter electrocardiography, initially revealing tachycardia. Propranolol treatment was started and improvement was observed. Observation of hypertrophic cardiomyopathy was conducted. Given the neovascularization changes in the right eye, the consultant ophthalmologist suggested. Coast disease, and recommended the child for laser treatment. Surgery was performed under general anesthesia on day 26 after birth. The treatment and perioperative period went without complications.

The new-born was initially fed by means of a tube. Castillo-Morales rehabilitation techniques, including motor silence, were used because there was no coordination of suction, swallowing and breathing. After six weeks the baby was fed with a nipple alternating with a tube, however, at 13 weeks of age, only a nipple was used. During the stay on the ward, the child was consulted by a neurologist and geneticist because either Noonan or Costello syndrome was suspected. The results of the examinations for Congenital Disorders of Glycosylation (CDG) syndromes were negative. Examination of the urine organic acid profiles using gas chromatography-mass spectrometry (GC-MS) did not show any neonatal metabolic defects.

Multi-directional rehabilitation using Bobath Neurodevelopmental Treatment (NDT) and Castillo-Morales Orofacial Regulation Therapy (OFRT) was used on the hospital ward. Before discharge from the hospital, the infant sucked slowly, drank 60 ml of milk, and was fed every two and a half hours on the mother's milk and modified milk. After 63 days of hospitalization, the patient was discharged home (Figures 1,2).

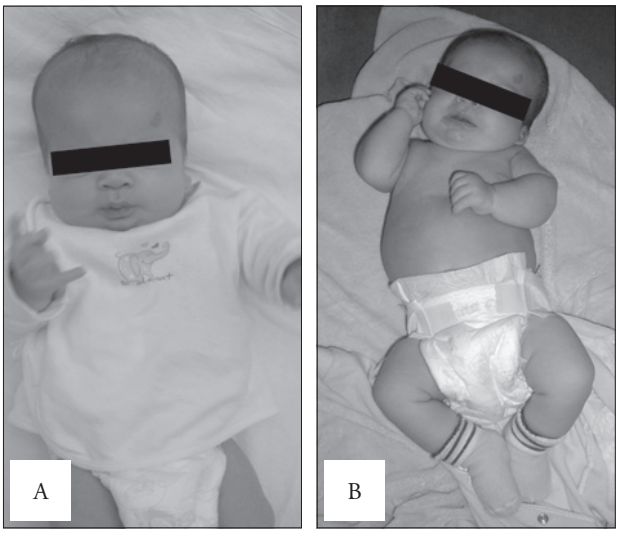

Figure 1. 2 months of life (A) and 2.5 months of life — lying on the back (B)

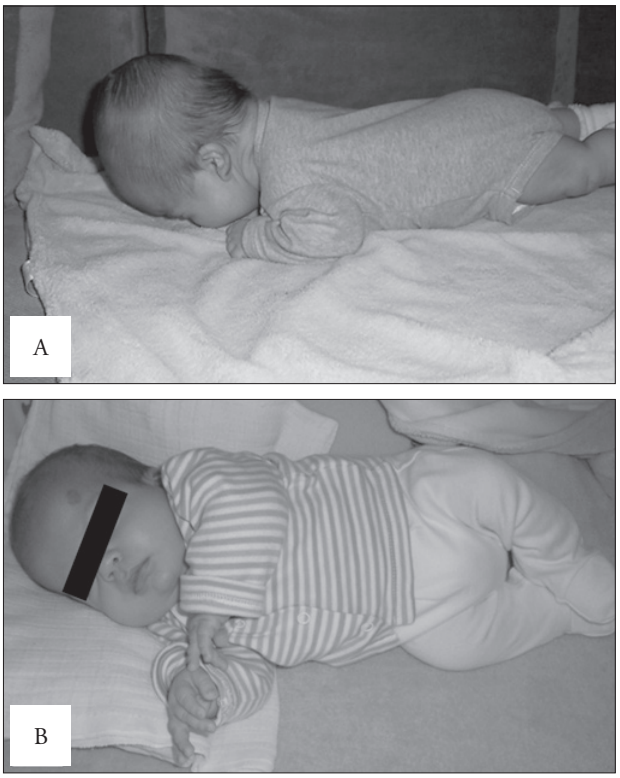

Figure 2. 3 months of life — lying on the stomach (A) and lying on the side (B)

Motor and Linguistic Development

As part of speech therapy, respiratory exercises named 'motor silence' were performed on the basis of Castillo-Morales OFRT intervention techniques. Lying on the back, belly and side were recommended, and the parents were provided with advice on proper care, carrying, lifting and bottle feeding, as well as suggestions for visual, auditory and sensory perception exercises.

The child's development was assessed using the Munich Functional Developmental Diagnostics (MFDD). It's a globally recognized, well-grounded method of early diagnostics applied for multi-faceted evaluation of psychomotor development in children at the age from the first month to the sixth year of life. In order to highlight the holistic approach to the child psychomotor development, MFDD is called a system of early diagnosis. The main aim of the MFDD is a complex evaluation of the child psychomotor development with which it is possible to diagnose potential disorders (e.g. in the scope of perception, speech development, social contacts or motor functions). MDFF is a quantitative method which shows the convergence (or divergence) of an examined child with patterns observed in 90% of children at the same age, evaluated as within the standard. It's the basis for taking appropriate therapeutic actions [12].

The child reacted very well to the voice of his parents, especially to the sight and voice of the mother, to which the child responded with a social smile and relatively

rich vocalization. When lying on his back the boy was not always stable on the ground, and his weight was shifted to the right. The left side remained shortened at the sternocleidomastoid muscle. The short and slightly sunken chest reduced respiratory, digestive and swallowing functions. The biggest problem was the mobility of the shoulders and the rotation of the head. The boy struggled to maintain his position on his belly. At the age of 3 months, the child was hospitalized twice due to respiratory infection caused by Respiratory Syncytial Virus (RSV).

At the age of 4 months, clinical trials were conducted at the pediatric cardiology department. Microcytic anemia was reported. A heart ultrasound showed left ventricular hypertrophic cardiomyopathy (no progressive features compared with the previous study), I-p leakage that was not hemodynamically significant, and Holter electrocardiography monitoring in the dominant sinus rhythm. Due to left ventricular hypertrophy, the dose of propranolol was increased.

In the molecular study, mutations in the RAF1 gene were identified. The detected lesion was pathogenic, and thus the examination confirmed the clinical diagnosis.

Figure 3. 5 months of life — grabbing and biting toys (A) and 6 months of life — grabbing feet (B)

At the age of 5 months, the boy made frequent attempts to manipulate his hands. When lying on his back, he put a toy in his mouth, and his hand at that time was usually open. The boy occasionally held his half-open hand in a higher position towards the object in front of him (Figure 3).

At the age of 6 months, he braced on his hands while lying on his belly, tried to reach for a toy, and even rotated in the horizontal plane. However, the features of muscle contraction and limited rotation on the right shoulder forced the baby to change position on his abdomen.

While lying on his back, he grasped his feet with his hands and tried to bring them closer to his mouth. Good visual coordination was observed, and his hands were used in asymmetrical and symmetrical body movements.

At the age of 9 months, a series of cranial ultrasound scans were performed revealing post-episode intraventricular hemorrhage. The cerebrospinal subarachnoidal fluid space was widened on both sides. In the abdominal ultrasound examination in the area of the spleen cavity, an additional spine with a diameter of 0.35 cm was shown. The psychomotor evaluation revealed very good visual and auditory perception. In terms of nutritional functions, he was able to chew and drink from a teaspoon. He tried crawling back and forth on his belly (Figure 4).

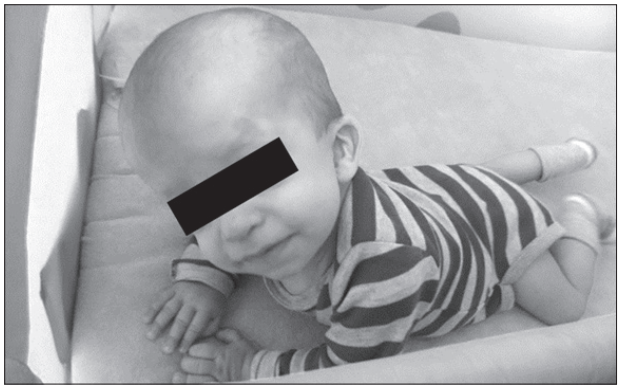

Figure 4. 9 months of life — lifting head on belly in forearm support

At the age of 13 months, the boy tried to sit on his own, but due to lack of proper balance, he required additional support. Hypoplasia of the corpus callosum has been shown in the head ultrasound examination. The ventricular rate was 40% on the right and 51% on the left, and enlargement compared to previous studies was noted. Due to his large head, his sitting position required support using special cushions. At 17 months of life, the surgery for cryptorchidism was performed. Thyroid examination indicated hypothyroidism, which was treated pharmacologically with euthyrox (Figures 5–7).

At 18–19 months of life, the boy began learning to walk. In terms of speech development, he has progressed to two-word phrases. He could imitate the sounds of animals and objects and name them. He could point his fingers at objects, put a smaller mold into a larger one, was able to select shapes and match the shape of the mold, and could find objects hidden under a box. He used the words dad and mom to identify people and could wave goodbye. He spoke intelligently (e.g. ball).

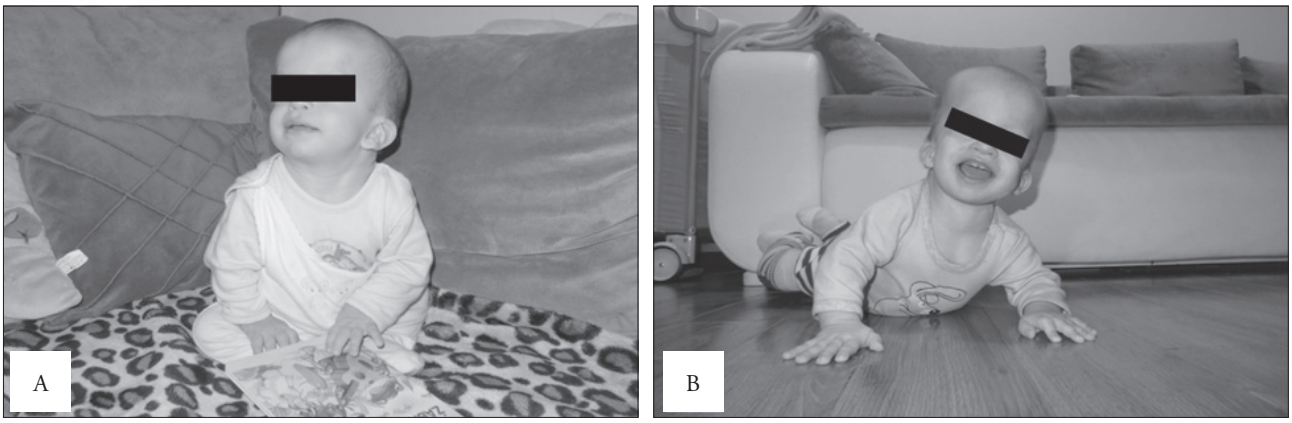

Figure 5. 13 months of life in sitting position (A) and lying on the belly on the forearms (B)

Figure 6. 15 months of life during play on the belly in with one-handed support on the forearm

Figure 7. 16 months of life in a kneeling position with furniture support (A) and 18 months in a two-feet standing position with a walker

Figure 8. 19 months of life in a sitting position (A) and 22 months in a kneeling position without support (B)

Figure 9. 23 months of life in standing position on his own

The child was characterized by very well developed sensory integration (Figure 8).

At 23 months of age, the child was able to walk. The boy was also able to follow commands, e.g.: "pick up", "put down". He was able to feed, he took himself a spoonful of food, was able to eat with his hands, made attempts to drink from a little cup, wipe his hands briefly, take off his shoes and hat, use a potty. In terms of a speech, he understood the meanings of words such as: cold, warm, big and small. He could to point parts of his body and name them. He could state his wishes. He could verbally refuse to execute a command by saying "no" (Figure 9).

At the age 26 months, the boy was treated in the pediatric ward for respiratory failure during RSV infection. He was admitted to the ward due to gastrointestinal obstruction, gastrointestinal decompression was performed, a large amount of fecal content without admixtures and gases was produced, abdominal distention was reduced, and an antibiotic was administered. The child was fed externally and intravenously with good tolerance. As a result of the treatment was disconnected from the respirator. A transcranial ultrasonography was performed in which a small degree of hydrocephalus was found for the right hemisphere (40%) and middle-degree hydrocephalus for the left hemisphere (50%). His condition subsequently improved and he was discharged home.

At 31 months of age, an MRI of the cervical spine was performed with contrast. An intraspinal hyperintense tumor containing three cystic spaces was found. A tumor was 4.1 centimeters in length and extended the length of the C5 to Th2 vertebrae, widening the spindle spinal cord and reducing the spinal fluid reserve. The MRI revealed an astrocytoma (pilocytic astrocytoma?). After consulting a neurosurgeon, a date for admission to the Children's Neurosurgery Clinic was established for further treatment.

Currently, the child is 36 months old and presents psychomotor development appropriate for the age of a healthy child (Figure 10).

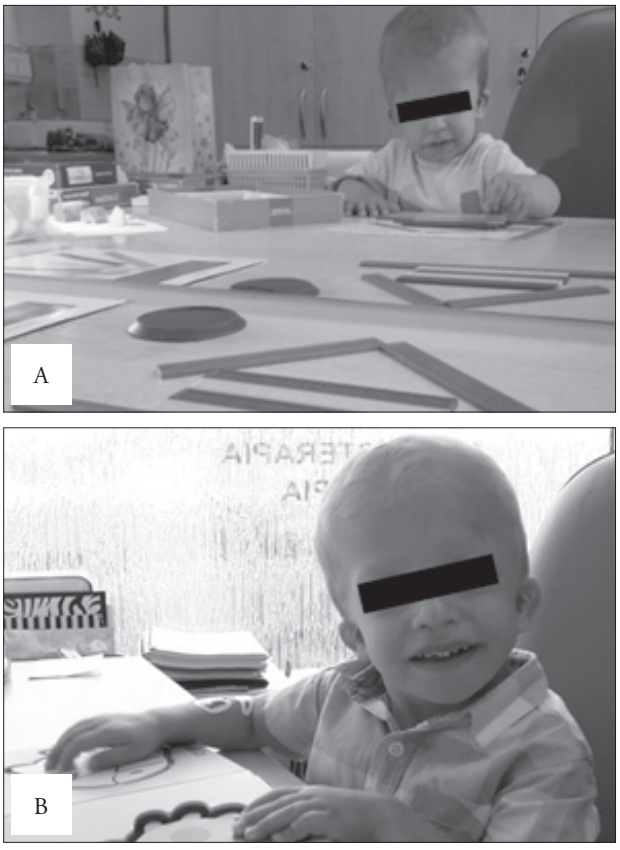

Figure 10. 31 months of life (A) and 36 months of life (B) seated during artistic works

Discussion

Management of NS should be comprehensive and multidisciplinary, and continuous monitoring of patients is crucial [13]. Examination of the cardiovascular system is recommended (cardiologic examination, electrocardiography, and echocardiography), as well as a clinical and radiological assessment of the chest and spine. Developmental evaluation with anthropometric measurements (especially growth monitoring), gastroenterological examination (gastroesophageal reflux), audiological, ophthalmological, hematological, and systematic urogenital examinations should also be performed [2,14,15].

Both caregivers and medical staff should follow the guidelines for children with NS. It is worth mentioning that a worldwide organization that supports patients and their families is the Noonan Syndrome Support Group (NSSG) [2,16].

In cases of problems with feeding, a neurologopedist's support may be helpful. This is particularly important because feeding problems, especially during infancy, can lead to calorie deficiencies and poor growth [16].

Although a number of patients experience learning difficulties and a mild form of mental impairment, the diagnosis of NS does not predispose to mental disorders [17,18]. The assessment and work of a speech therapist are also necessary due to disturbances in the development of communication competencies [19,20]. As shown in

a previous study, children, and adolescents with NS do not have a single consistent pragmatic profile; however, 76.5% of participants in a study of pragmatic speech disorders showed communication disorders, and the pragmatic ability of children with NS was significantly lower than in the control group [21].

Conclusions

NS is a multi-symptomatic disease that manifests itself in the expression of clinical symptoms requiring the interdisciplinary cooperation of many specialists. Patients with NS should be covered by multi-specialty medical care from birth, and because of the clinical and genetic heterogeneity of the syndrome, doctors and therapists should be aware of the complexity of this disorder. It should be pointed out that in many cases cardiosurgical intervention is required. The decisive factor for the further development of the child and the planning of specialist care is the rapid identification of the disease. The fact is that the identified mutation in the RAF1 gene in patients with NS does not mean they are predestined to develop psychomotor disorders [22,23].

References

[1] Lepri F.R., Scavelli R., Digilio M.C. et al. Diagnosis of Noonan syndrome and related disorders using target next generation sequencing. *BMC Med Genet*. 2014; 15:14.

[2] Bhambhani V., Muenke M. Noonan syndrome. *Am Fam Physician*. 2014;89(1):37–43.

[3] Bezniakow N., Gos M., Obersztyn E. The RASopathies as an example of RAS/MAPK pathway disturbances — clinical presentation and molecular pathogenesis of selected syndromes. *Dev Period Med*. 2014;18(3):285–296.

[4] Cizmarova M., Kostalova L., Pribilincova Z. et al. Rasopathies — dysmorphic syndromes with short stature and risk of malignancy. *Endocr Regul*. 2013;47(4):217–222.

[5] Tidyman W.E., Rauen K.A. Noonan, Costello and cardio-facio-cutaneous syndromes: dysregulation of the Ras-MAPK pathway. *Expert Rev Mol Med*. 2008;10: e37.

[6] Tartaglia M., Pennacchio L.A., Zhao C. et al. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. *Nat Genet*. 2007;39(1):75–79.

[7] Gos M., Leszkiewicz M., Abramowicz A. RAS/MAPK signal transduction pathway and its role in the pathogenesis of Noonan syndrome. *Postepy Biochem*. 2012;58(3):255–264.

[8] Malaquias A.C., Brasil A.S., Pereira A.C. et al. Growth standards of patients with Noonan and Noonan-like syndromes with mutations in the RAS/MAPK pathway. *Am J Med Genet A*. 2012;158A(11):2700–2706.

[9] Yaoita M., Niihori T., Mizuno S. et al. Spectrum of mutations and genotype-phenotype analysis in Noonan syndrome patients with RIT1 mutations. *Hum Genet*. 2016;135(2):209–222.

[10] Nemcikova M., Vejvalkova S., Fencl F., Sukova M., Krepelova A. A novel heterozygous RIT1 mutation in a patient with Noonan syndrome, leukopenia, and transient myeloproliferation-a review of the literature. *Eur J Pediatr*. 2016;175(4):587–592.

[11] Thompson D., Patrick-Esteve J., Surcouf J.W. et al. RAF1 variants causing biventricular hypertrophic cardiomyopathy in two preterm infants: further phenotypic delineation and review of literature. *Clin Dysmorphol*. 2017;26(4):195–199.

[12] Markiewicz K., Pachalska M. Diagnosis of severe developmental disorders in children under three years of age. *Med Sci Monit*. 2007;13(2):CR89–99.

[13] Tafazoli A., Eshraghi P., Koleti Z.K., Abbaszadegan M. Noonan syndrome — a new survey. *Arch Med Sci*. 2017; 13(1):215–222.

[14] Roberts A.E., Allanson J.E., Tartaglia M., Gelb B.D. Noonan syndrome. *Lancet*. 2013;381(9863):333–342.

[15] Sullivan P.B. Gastrointestinal disorders in children with neurodevelopmental disabilities. *Dev Disabil Res Rev*. 2008;14(2):128–136.

[16] Romano A.A., Allanson J.E., Dahlgren J. et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010;126(4):746–759.

[17] van der Burgt I. Noonan syndrome. *Orphanet J Rare Dis*. 2007;2:4.

[18] Şıklar Z., Genens M., Poyrazoğlu Ş. et al. The Growth Characteristics of Patients with Noonan Syndrome: Results of Three Years of Growth Hormone Treatment: A Nationwide Multicenter Study. *J Clin Res Pediatr Endocrinol*. 2016;8(3):305–312.

[19] Roelofs R.L., Janssen N., Wingbermühle E., Kessels R.P., Egger J.I. Intellectual development in Noonan syndrome: a longitudinal study. *Brain Behav*. 2016;6(7):e00479.

[20] Pierpont E.I., Ellis Weismer S., Roberts A.E. et al. The language phenotype of children and adolescents with Noonan syndrome. *J Speech Lang Hear Res*. 2010;53(4): 917–932.

[21] Selås M., Helland W.A. Pragmatic language impairment in children with Noonan syndrome. *Clin Linguist Phon*. 2016:30(11):899–910.

[22] Roelofs R.L., Wingbermühle E., Freriks K., Verhaak C.M., Kessels R.P., Egger J.I. Alexithymia, emotion perception, and social assertiveness in adult women with Noonan and Turner syndromes. *Am J Med Genet A*. 2015;167A(4):768–776.

[23] Wingbermühle E., Roelofs R.L., van der Burgt I. et al. Cognitive functioning of adults with Noonan syndrome: a case-control study. *Genes Brain Behav*. 2012;11(7):785–793.

Corresponding Author:
Robert Dymarek
Department of Nervous System Diseases
The Faculty of Health Sciences
Wrocław Medical University,
Bartla Street 5, 51-618 Wrocław, Poland
e-mail: r.dymarek@gmail.com

Conflict of Interest: None
Funding: None
Author Contributions: Teresa Kaczan[A–I], Robert Śmigiel[A–I], Magdalena Kazimierska-Zając[A–H], Robert Dymarek[F–H], Joanna Rosińczuk[A–I]
(A — Concept and design of research, B — Collection and/or compilation of data, C — Analysis and interpretation of data, D — Statistical analysis, E — Writing an article, F — Search of the literature, G — Critical article analysis, H — Approval of the final version of the article, I — Acquisition of assets [eg financial])
Received: 22.02.2019
Accepted: 19.03.2019