CASE STUDY

ACTA Vol. 18, No. 4, 2020, 525-535
NEUROPSYCHOLOGICA

Received: 07.02.2020
Accepted: 01.10.2020

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

DIAGNOSIS OF CHILDREN WITH SANFILIPPO DISEASE – PSYCHOLOGICAL, SOCIAL AND MOTOR ASSESSMENT

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SUMMARY

Background: Sanfilippo disease (mucopolysaccharidosis, MPS IIIA) is one of the types of mucopolysaccharidosis associated with extensive neurological effects and somatic symptoms. The consequences of neurodegeneration and cognitive impairment are manifested in challenges with the daily functioning of patients who experience problems with communication and following instructions. The aim of this study was to assess the cognitive functioning of three patients with MPS IIIA and to find patterns of neurodegeneration and to make their environment more friendly.

Material/ Methods: Three boys (from 5.5 to 7 years) with MPS IIIA participated in the study. Each participant attended two meetings, and his functioning was assessed by three independent person (using two-way mirror). We used Bayley's Scale III with some modifications. Interviews with parents were also included.

Results: The communication of patients was limited to some vocalizations. Patients presented instrumental use of items, but not all of them were able to repeat actions after diagnostician or presented object permanence. The results showed that the cognitive functioning of participants was significantly hindered by problems related to motor dysfunction, hyperactivity, and ataxia. The psychological data was collated with medical results.

Conclusions: This study allows indicating new sources giving the possibility of child phenotype variability and to create specific interventions in the field of psychological therapy for patients with MPS IIIA and their families.

Key words: Bayley's Scale III, cognitive functioning, rare disease, qualitative research

INTRODUCTION

Sanfilippo disease (mucopolysaccharidosis type III or MPS III) is one of several recognized types of mucopolysaccharidosis. It is caused by mutations in one of four different genes coding for enzymes involved in the degradation of heparan sulfate (HS), one of the glycosaminoglycans (GAGs). Thus, four subtypes of this disease are distinguished (MPS IIIA, IIIB, IIIC, and IIID). MPS III is a rare disease, inherited in an autosomal recessive pattern (all subtypes); it belongs to the class of lysosomal storage diseases (LSD). The accumulation of HS results in progressive impairment of affected tissues (Neufeld, Muenzer, 2001). All subtypes of the disease are considered clinically synonymous, and the symptoms and course of the disease are similar, despite differences at the genetic, biochemical, and metabolic levels (Wegrzyn et al., 2010; Wegrzyn et al. 2018).

Unlike the other types of MPS, Sanfilippo disease is associated with extensive neurological effects and mild somatic symptoms (Shapiro et al., 2016). The estimated frequency of occurrence of MPS III is 0.28-4.1/100,000 births, depending on the geographical region. This prevalence makes MPS III the most frequent of mucopolysaccharidosis diseases (Wijburg, Wegrzyn, Burton, Tylki-Szymanska, 2013). Progression of MPS III is correlated with the accumulation of GAG, particularly HS (Valstar, Marchal, Grootenhuis, Colland, Wijburg, 2011), resulting in the degeneration of the central nervous system (CNS) (Fedele, 2015). Different abnormalities in HS distribution and content occur and influence changes in postsynaptic functions (Dwyer et al., 2017). Furthermore, in some patients, the accumulation of glycolipids is observed in Purkinje cells and neurons, which results in changes in the patients' functioning (Kowalewski et al., 2014). Children with MPS III are born without any symptoms, and the diagnosis is often delayed until the 2nd–4th year of life (Burhman, Thakkar, Poe, Escolar, 2014). Speech delay—associated with a reduction in hippocampal volume – is typically the first symptom and appears before cognitive deficits (Shapiro et al., 2016). This delay can cause some emotional and social problems within the first 2–4 years of life, leading to MPS III is frequently misdiagnosed as an autism spectrum disorder or attention deficit and hyperactivity disorder (Wijburg et al., 2013).

The symptoms which occur after the second year of life include coarse facial features; enlarged tongue; hepatomegaly (Buhrman et al., 2014); behavioral disorders (Wijburg et al., 2013); epilepsy; impairment of vision and hearing; frequent infections of the throat, ear, and nose; diarrhea (Valstar Ruijter, van Diggelen, Poorthuis, Wijburg, 2011; Andrade, Aldamiz-Echevarria, Llarena, Couce, 2015); and sleeping problems (occurring in more than 70% of patients Bax, Kumar, Ghosh, De, Basu, 2013). Sleep problems manifest in daytime sleep duration and longer sleep onset latency (Mahon et al., 2014). Cases of hearing impairment have also been reported (Barik et al., 2012).

Behavioral problems include hyperactivity and expression of frustration, with tantrums being most frequently reported. Tantrums are often misinterpreted as

destructive, aggressive behavior (Cross, Hare, 2016). A lack of fear is also noted in patients with MPS IIIA; this is associated with atrophy of the amygdala in the brain (Shapiro et al., 2016). Behavioral problems also include perseverative chewing/hyperorality. These symptoms are very challenging for a family and impose a burden on its members. They can lead to exhaustion (physical and mental), sleep deprivation, social isolation, and financial problems (Grant et al., 2013). Parents of children with MPS III also demonstrate high levels of anxiety and depression (34.6% of mothers and 36.8% of fathers; Conijn, Nijmeijer, van Oers, Wijburg, Haverman, 2019).

Patients with MPS IIIA can develop adaptive abilities until their 4th year of life, at which point these capacities begin to decrease (Shapiro et al., 2016). As the disease progresses, there is a decline in cognitive functioning, leading to dementia. Severe CNS degeneration typically results in death within the second or third decade of life (Valstar, Ruijter, van Diggelen, Poorthuis, Wijburg, 2008). In patients with MPS IIIA, extended ventricular volume, and a decrease in cortical grey matter and size of the amygdala are noted (Shapiro et al., 2016). The speed of this process varies. Usually, however, patients become entirely dependent on their environment in the second decade of life and die in the third decade of life, although cases of longer survival are known (Valstar et al., 2011; Andrade, et al. 2015).

There is no cure for this disease (Gaffke, Pierzynowska, Piotrowska, Wegrzyn, 2018). There are some potential treatments for MPS III, for example, enzyme replacement therapy (ERT), substrate reduction therapy (SRT), and gene expression-targeted isoflavone therapy (GET IT). The third treatment, GET IT, may be effective and inhibit or slow down the progression of the disease in some patients (Piotrowska et al., 2011). However, despite correction of both biochemical parameters (Malinowska et al. 2009) and behavior (Malinowska et al., 2010) of MPS IIIB mice, and biochemical improvement in patients during the placebo-controlled studies (de Ruijter et al., 2012), the clinical benefit is still not clear, and the results of phase 3 clinical trial await publication (Wegrzyn et al., 2018).

The consequences of neurodegeneration and cognitive impairment are reflected in problems with the daily functioning of patients. They experience problems with communication and following instructions (including instructions from parents). Moreover, patients present maladaptive behaviors. This is also accompanied by impairment of motor skills (Escolar et al., 2017; Shapiro, Jones, Escolar, 2017; Shapiro et al., 2016; Burhman et al., 2014; Piotrowska et al., 2011). However, details of the cognitive abilities of patients suffering from Sanfilippo disease are still unknown, most probably due to failure of the classical test to measure certain parameters in these specific patients, and thus, advice regarding environmental conditions optimal for these patients are mostly unknown.

The aim of the research was to analyze three case studies of children with the same type of the Mucopolysaccharidosis (MPS IIIA) for the possibility to find patterns of their functioning and to find injunctions to improve their everyday living.

CASE STUDIES

Participants

Children with Sanfilippo syndrome (*n*=3, all boys; MPS IIIA, Mc Kusick's OMIM no. 252900) and their parents were asked to participate in the study. The aim was to estimate the children's physical and cognitive functioning at different stages of MPS IIIA.

Case 1 – boy, 5,5 years

The first admission to the clinic took place at the age of 2 years and 8 months was admitted to the clinic because of hepatomegaly and dysmorphic features.

The child was born at term by a cesarian section after normal pregnancy; birth weight was 3,1kg; head circumference at birth was 34cm. Neonatal examination revealed umbilical hernia.

Head control was achieved by the 3rd month of life, autonomous walking by the 18yh month of life. He communicates with single words. Recurrent respiratory tract infections were reported from the 2nd month of life. Adenotonsillar hypertrophy was diagnosed; the child was waiting for the adenotonsillectomy procedure.

Clinical examination revealed height and weight in the normal range, head circumference above 97centile, coarse face, hands with stiff, curled fingers, heart murmur, hepatomegaly (the lower hepatic margin was 2cm below the costal arch). Ultrasound examination revealed enlarged spleen volume and aortic valve insufficiency.

An enzymatic test revealed a low activity of heparan-N-sulfatase.

Case 2 – boy, 6 years

The first admission to the clinic took place at the age of 4, because of behavioral disturbances followed by an arrest of mental and motor development. Parents reported problems with language delay and language regression, poor interest in playmates, and toys at playschool. They were also concerned about toilet training regression.

The boy was born by a cesarian section after high-risk pregnancy (antepartum bleeding at 25 weeks of pregnancy) in term; birth weight was 4,6kg.

Early psychomotor development was within normal limits, autonomous walking and verbal communication with single words only were achieved by the 14th month of life. Clinical examination revealed normal height and weight, thickened skin with mild hypotrichosis (especially on the back and extensor limb surfaces), the hair was wiry. The bridge of the nose was slightly depressed, thick eyebrows, slightly enlarged mouth, and tongue. Hepatosplenomegaly (lower hepatic margin 3cm below the costal arch, spleen 1cm below the costal arch) was confirmed by ultrasound examination. The heart was normal (confirmed by ultrasound examination). The physical examination also revealed a mild joint limitation.

The quantitative urinary analysis showed that the total glycosaminoglycans (GAGs) were above the normal range, GAGs were composed mainly of heparan sulfate. An enzymatic test revealed a low activity of heparan-N-sulfatase.

Case 3 – boy, 7 years

The first admission to the clinic took place at the age of 4, because of dysmorphic features and hepatomegaly. The child was born at 41hbd from spontaneous delivery after uncomplicated pregnancy;

birth weight was 3,5kg; the perinatal period was uncomplicated. Motor development was normal: autonomous walking was achieved by the 14th month of life. Delayed speech development – speech therapy was introduced.

Clinical examination revealed psychomotor delay, slurred speech, coarse face, wiry hair, large tongue, adenoids hypertrophy, hepatosplenomegaly (the lower hepatic margin was 3cm below the costal arch, the spleen 1cm below the costal arch). Ultrasound examination confirmed an enlarged liver and spleen volume. An enzymatic test revealed a low activity of heparan-N-sulfatase. The genetic testing confirmed the diagnosis. At the age of seven, he developed epileptic seizures.

Instrumentations and Procedure

Each participant attended two meetings, and firstly the interview with parents was committed to establishing the start point of the examination.

The Bayley's Scale III (BSID III) was used to estimate the cognitive functioning of the three boys.

Tasks from various stages of the test were given to the boys. During the first meeting, it was decided to begin with tasks for children at 19 months and 16 days of age.

After observations made at the first meeting, the researchers decided not to use the complete BSID III and to implement some modifications to make the material more accessible to children with Sanfilippo disease. It was decided only to use tasks from the Cognitive Scale.

Furthermore, observation of social, emotional, and motor functioning was conducted during these meetings by three independent observers using a two-way mirror.

Data analyses

The obtained data were analyzed by three independent psychologists. One of them was in contact with the patient and was carrying out the diagnosis process. His data were collected after the meeting. The other two observed the diagnosis according to the one-way mirror. All of the collected information was discussed and analyzed together.

RESULTS

The results obtained regarding cognitive functioning were collated with other aspects of the functioning of the children. Table 1 shows the most important aspects of the social functioning of patients with MPS IIIA.

All patients maintained eye contact for at least 30 seconds. Patients maintained eye contact during the issuing of commands, the presentation of new objects, and when eating.

Two patients reacted to their name and were able to concentrate on the prosodic aspects of speech and to react to them with curiosity, vocalization, or mimicry. Patients presented communication of their needs and used some vocalizations and gestures to communicate. They also presented individual echoic words.

Moreover, all patients presented reactions to frustration. Their reactions differed, but they were clear enough to identify. Only one patient showed engrossment – in contrast to the others, there were no problems with arousing his interest (especially when a new object was introduced).

Aspects of cognitive functioning (Table 2) were divided into three groups: attention, memory, and thinking. We present a qualitative summary of the patients' functioning without quantitative presentation of scores because of the modifications to the tools and the tailoring of the diagnostic assessment.

The results regarding attention are summarized in terms of 3 basic skills: orientation, attentional maintenance, and inhibition. As shown in Table 2, there were problems with the adaptation of the measures of attention (different strategies for arousing focus were needed); not all patients were able to concentrate for a long time. Furthermore, as previously mentioned, the inhibition of reactions was very difficult for these patients.

Despite the fact that there were several problems with measuring memory (due to attention deficits), it was found out that two patients recognized the place/people/episodes at the second meeting (after one week). In one patient

Table 1. The social functioning of the patients with MPS IIIA.

Parameter	Patient's results		
	1	2	3
Eye contact	Maintained eye contact.		
Reaction to name	Sometimes.	No reaction.	
Focus on diagnostician	Concentration on the prosodic aspects of speech.	No focus.	
Needs Communication	Guessed by diagnostician: vocalization, eye fixation, sometimes pointing.	Guessed by diagnostician: vocalization, sometimes pointing.	Clear, sudden: pointing, vocalization, eye fixation.
Communication	Some vocalization (non-specific).	Limited to the sounds: "Bum", "no", and "yeah".	A lot of vocalization with prosody and gestures (e.g., threatening with a finger).
Reactions to frustration	Active avoidance	Sudden	

Table 2. The cognitive functioning of the patients with MPS IIIA

Parameter		Patient's functions		
		1	2	3
Attention	Orientation reflex	None.		
	Maintenance of attention	20 minutes; location, prosody, and volume changes were needed.	A few minutes; a lot of breaks were needed.	Over a dozen minutes, mother's help was needed
	Inhibition of reactions	Little difficulty, some perseverations.	A lot of difficulties, a lot of perseverations.	Moderate difficulty, some perseverations
Memory		Some aspects of long term memory (place, episodes)	Could not be measured (too many deficits).	Long term memory: place, episodes, moderate memory of people, objects
Thinking	Object permanence	Present.	None.	Present.
	Instrumental use of items	Present.	Present.	Present.
	Repetition	He repeated the activities after the diagnostician.	None.	he repeated the activities after the diagnostician
	Matching shapes	Could identify identical elements.	Could identify identical and missing elements.	Same, missing elements and making a collection of elements

(thanks to preserved repetition skills), it was possible to measure elements held in working memory.

Moreover, two patients presented the development and no impairment in understanding object permanence. All patients showed instrumental use of items (e.g., using a stick to bring an object of interest closer) and matching shapes (not without difficulties and preferences for some figures over others).

DISCUSSION

The results presented above showed the dynamic and course of the disease. They showed how patients perform in the field of psychosocial functioning along with the presentation of the medical condition. All patients presented a slight delay compared to healthy children in acquiring speech and walking skills (Shaffer, 2010).

Unfortunately, the estimation of functioning in some areas was significantly hampered by problems related to motor dysfunction, hyperactivity, and ataxia. While performing tasks, some patients were able to pay attention for a short time, but, after a while, disturbances distracted the patients from the task at hand. However, the patients were able to perform simple transformations and find sim-

ple patterns in interlocking shapes. They also demonstrated basic memory functions. Patients worked better with people, in places, and with objects to which they have previously been exposed (Grant et al., 2013).

The youngest patient (case 1) had presented better cognitive functioning than others. He was the only one who reacted to his name, was focused on diagnostician, and presented avoiding reaction to a stimulus, causing frustration. Moreover, he had fewer difficulties in the inhibition of the reactions and could maintain attention for a longer period than others.

Regarding cognitive functioning, it can also be noticed that the second patient presented more severe disturbances than others. It is necessary to underline that it is not the oldest patient. Their parents report more developmental problems at the point of the diagnosis than others. Moreover, it was the only patient with disturbances in the perinatal period (high-risk pregnancy – antepartum bleeding at 25 weeks). It is important to notice that maternal prenatal distress predict lower cognitive abilities (ex. Schechter at al. 2017). Maternal bleeding during pregnancy is also one of the risk factors of impaired cognitive functioning (Milberger, Biederman, Faraone, Guite, Tsuang, 1997). Moreover, the existence of rare genetic disease and perinatal complications can provide a different rate of progression of the disease.

No patterns of impairment in communication and functioning of memory were presented. There is not any link with the age, actual medical condition, or medical history. This implies the need to look at the results of genetic testing as well as the need to look for factors in the environment that may affect the abilities and condition of these patients.

It is worth mentioning that in Sanfilippo disease patients are dealing with various negative effects of the disease, but also with the overlaping of different symptoms. There are several studies wchich indictate the corelation between cognitive impairment and cardioogical problems (*Case 1*;i.e.)or epilepsy (*Case 3;* i.e.Mefford, 2014; Mazurkiewicz-Bełdzińska, Szmuda, Pilarska, Matheisel, 2015).

This work focused on the functioning of patients with MPS III in diagnosis situations as well in everyday life. In this context, it is essential to find ways to reduce the number and intensity of maladaptive behaviors, leading to a better assessment of the patients' situations. It is possible to modify patients' behaviors and adjustment to situations because attenuation of behavioral symptoms in familiar places has been observed (Escolar et al., 2017). Adaptation can be more difficult in an unknown environment, spending mental resources to adapt to a new place might diminish their capacity to display cognitive abilities.

The examination was attended by the diagnostician to modify the positioning and location of different tasks. The position of the presented object in the child's visual field was also modified based on the patient's reactions. Positioning objects in the child's line of sight reduced excessive stimuli in the environment. Positioning objects centrally in the patient's line of sight is likely optimal. Breaks were adjusted according to the state of arousal and the patient's attention (hyperactivity, attention problems, increased fatigability) and also because of the fragmented, se-

lective increased tension of particular muscle groups. The literature also mentions that if behavioral problems are triggered by a specific situation (e.g., a new place) or unpleasant feelings (e.g., pain), it is important to identify these stimuli and prevent them before undesirable behaviors occur (Grant et al., 2013).

Furthermore, the creation of environments with structured schedules and routines could provide a safe place for these patients and hence, could reduce the number of behavioral problems (Grant et al., 2013). In terms of cognitive functioning, basic attention reflexes, and basic contact (in the visual and gestural areas) were both observed in the patients.

These results motivate the search for the optimal conditions for the functioning of people with MPS IIIA in everyday situations, intending to identify ways of organizing spaces to minimize cognitive disturbances. This research allows the design of specific interventions in the field of psychological therapy for patients with MPS IIIA and their families —an area that certainly requires further research, particularly into the best ways in which to interact with such patients. The conclusions from several research are similar (ex. Bidzan, Koszewska, Bielenninik, 2013; Jankowska, Włodarczyk, Campbell, Shaw, 2015) – these families require particular support with should include the functioning of entire family system and moreover should be designed with consideration of family`s available resources.

List of abbreviations

MPS – mucopolysaccharidosis
BSID III – Bayley's Scale III

Ethical considerations

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained from all patients for being included in the study. This study obtained the consent of the ethics committee of the Institute of Psychology, University of Gdansk, Poland (11D/2018).

Acknowledgments

We want to thank the parents who participated in the study with their children. Authors Anikiej Paulina, Agata Rudnik, Monika Limanowka, Jolanta Wierzba, and Arkadiusz Manski declare that they have no conflict of interest.

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