Early clinical signs in lysosomal diseases

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Abstract

Background and aim. The lysosomal storage diseases are a group of monogenic diseases with multisystemic impairment and chronic progression induced by the deficiency of lysosomal acid hydrolases involved in the breakdown of various macromolecules. The accumulation occurs in the macrophages of the reticule-endothelial system and causes enlargement and functional impairment. The mainly involved organs are the brain, liver, spleen, bones, joints, airways, lungs, and heart. The aim of this study was to evaluate early symptoms, signs and the delay in the diagnosis of different lysosomal diseases.

Methods. The medical documentation of 188 patients with lysosomal storage disorders, aged 1-70 years, were analyzed. All these patients were specifically diagnosed, by enzyme and molecular assay.

Results. The age of clinical signs onset varies in different type of lysosomal diseases, from the first months of life or early childhood in severe form, to adulthood in attenuated forms. The delay between the clinical signs onset and specific diagnosis ranged from 0.5 months to 57.91 years.

Conclusions. The lysosomal storage diseases are rare diseases with childhood onset, but these early signs and symptoms are not recognized and are often taken into account when the vital organs damage becomes manifest.

Keywords: lysosomal disease, early diagnosis

Background

The lysosomal storage diseases are a group of inborn errors of metabolism with multisystemic impairment and chronic progression, induced by the deficiency of lysosomal acid hydrolases involved in the breakdown of various macromolecules [1]. Normally these substances are degraded in the lysosomes into small molecules reusable by the cell [2]. If one of the 70 enzymes is deficient, the degradation and discharge of these substances cannot be achieved correctly [3]. Their abnormal accumulation in lysosomes leads to impairment of cellular function with the accentuation of apoptosis and finally to enlargement and/or functional impairment of the different organs and system. Mainly involved organs are the brain, liver, spleen, bones, joints, airways, lungs and heart [4].

According to the type of accumulated substances, seven categories of lysosomal disorders are distinguished: sphingolipidoses (Gaucher disease, Niemann-Pick disease, Fabry disease, gangliosidosis), mucopolysaccharidosis, glycoproteinosis (alpha mannosidosis, mucolipidosis type I), multiple enzyme deficits (mucolipidosis type II/III), lysosome transport deficits (cystinosis), glycogen storage disease (glycogenosis type II) and other lipidosis (Wolman disease) [4]. There are monogenic diseases with recessive autosomal transmission in most cases, exceptions are Hunter syndrome and Fabry disease [5,6]. Clinical features may include progressive neurological deterioration, dysmorphic features, organ enlargement, bone disease, heart and lung impairment. The affected infants usually appear normal at birth, the

DOI: 10.15386/mpr-2228

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clinical signs of these diseases are gradually developed as non-metabolized substrates accumulate in the body, thus depending on the severity of the enzyme deficiency and the organs in which toxic metabolites accumulate [3,4]. Symptomatology can start from the first months of life, in childhood or late in adulthood. The symptomatology of these diseases is nonspecific, reflecting the suffering of the affected tissues and organs, which may delay the diagnostic [7]. Investigations include non-specific tests addressed to organs and systems affected, such as biochemical, hematological and imaging assay (ultrasound, roentgenographic, magnetic resonance imaging). Specific enzyme and genetic studies are usually required to establish the exact diagnosis. For most disorders there is no specific therapy yet, although enzyme replacement therapy or bone marrow transplantation has been shown beneficial in several disorders [8,9].

• **Sphingolipidoses** and **lipid storage disorders** usually present with visceromegaly and progressive neurological impairment. In Gaucher disease, the severe splenomegaly and hepatomegaly are associated with anemia, cutaneous hemorrhagic syndrome (gingivorrhagia, epistaxis, bruising) and bone disease (bone crisis, chronic pain and pathological fractures) [10-12]. In Fabry disease, the pain and paresthesia, hypohydrosis, heat and cool intolerance, gastrointestinal dysfunction, angiokeratomas are the early signs with onset in childhood, but underdiagnosed [13-15].

• **Mucopolysaccharidoses (MPS)**. The affected children typically present coarse facial features, recurrent upper respiratory tract infections, hepatomegaly, splenomegaly, umbilical and inguinal hernias, joint stiffness, dysostosis multiplex, heart valve disease, progressive neurological deterioration with loss of milestones, corneal clouding and hypoacusia [16-18].

• **Oligosaccharidosis.** The main clinical features in alpha-mannosidosis are intellectual disability, ataxia, coarse face and dysostosis multiplex which are similar with the mucopolysaccharidoses [19,20] .

• **Mucolipidoses** combine clinical features of the mucopolysaccharidoses and sphingolipidoses and may reflect the deficiency of several lysosomal enzymes, because of defective enzyme processing [21].

• **Lysosomal transport defects.** These disorders result from defective transport out of lysosomes. Cystinosis causes nephropathy (Fanconi syndrome) and dysfunction of other organs including the thyroid gland and the eyes [22].

Aim of the study

To evaluate early symptoms and signs, and the delay in the diagnosis of patients with lysosome diseases evaluated in Centre of Expertise for Rare Metabolic Diseases – (Lysososmal Diseases) in Cluj-Napoca, during the period 2000-2020.

Subjects and methods

The medical documentation of 188 patients with lysosomal storage disorders, aged 1–70 years, were analyzed. All these patients were specifically diagnosed (enzyme and molecular assay). Clinical evaluation of the patients included standard auxological assessment, bone radiographs, magnetic resonance imaging, goniometry, neurological and psychological evaluation, otorhinolaryngology examination with audiogram, ophthalmological examination, cardiology evaluation (ECG, Doppler echocardiography) and spirometry. The tests were according to the particularities of each disease. The enzymes activity was determined by variable methods which were available at different times, plasmatic activity (Biochemistry Department of Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca) or dried blood spot by fluorometry (Centogene Laboratory Rostock and Hamburg Germany). Genetic testing was done respecting the ethical standards of the hospital committee, genetic evaluation was performed at Archimed Life Science GmbH Laboratory, Vienna and Centogene Laboratory, Rostock.

Results

Lysosomal diseases categories and clinical characteristics of the 188 patients are presented in table I.

The analysis of different lysosomal disorders showed:

In Gaucher disorders: 89 Gaucher patients aged between 2-69.91 years were analyzed. The average age of symptoms onset in type 1 was 15.74±13.2 years and 1.08±0.14 years in type 3, respectively. The signs at the onset were often the bruises or other hemorrhagic signs. Most of the patients presented anemic syndrome with various clinical intensity. All the 62 patients without splenectomy presented nasal and gingival bleeding of various frequency and intensity, moderate and severe thrombocytopenia. Twenty-seven patients underwent splenectomy, but the diagnosis was established in several cases years after this intervention (in one patient, the diagnosis was established 25 years after the splenectomy). Splenomegaly was registered in the remaining 62 patients. Hepatomegaly with various degrees was encountered in all 89 patients.

In Fabry disease: 51 Fabry patients were analyzed, aged between 11-80 years. The mean age of clinical sings onset was 12.65±28.2 years, but most patients were diagnosed many years later, after decades of treatment for different complications of the disease (renal failure, stroke, cardiomyopathy, chronic pain), the average delay in diagnoses was 36.35±21.25 years. Only in two patients belonging to families with history of Fabry disease, the diagnosis was established early, before irreversible damages occur.

Table I. Clinical characteristics of the patients with different categories of lysosomal disorders. F=female;M= male;

Disease	No.	Gender	Age (years)				Clinical signs										
		F/M	Onset	Specific diagnosis	Delay in diagnosis Mean	Limits	H	S	C	O	R	N	RE	HE	HM	O	HY
Gaucher diseaseType 1	86	52/34	15.74±13.2	29.9±14.93	14.59±14.3	0.5±57.91	+	+	-	+	+	-	-	-	+	-	-
Gaucher diseaseType 3	3	2/1	1.08±0.14	3.81±3.49	3.56±2.72	0.5±6.84	+	+	-	+	+	+	-	-	+	-	-
Niemann-Pick disease	5	4/1	1.8±5.33	4.24±2.15	3.25±4.55	0.25±7.5	+	+	-	+	+	+/-	-	-	+	+	+
Fabry disease	51	38/24	12.65±28.2	41.2±31.2	36.35±21.25	0.5-59.5	-		+		+	+	+	-	-	+	+
Pompe disease	11	6/5	10.09±10.9	23.65±22.41	12.41±12.99	0.16-28.5	+/-	-	+	+	+		-	-	-	+	+
MPS Type I	7	5/2	1.17±1.94	7.79±7.07	5.54±5.2	0.25-12.5	+	+	+	+	+	+/-	-	+	-	+	+
MPS Type II	23	-/22	1.48±2.71	5.12±4.3	2.9±2.88	0.25-11.6	+	+	+	+	+	+/-	-	+	-	+	+
MPS Type III	8	6/2	1.59±1.93	4.86±3.55	3.81±3.55	2.5-7.16	+	+	+	+	+	+	-	+	-	+	+
MPS Type IV	6	4/2	2.8±2.72	4.65±2.11	3.2±2.67	1.25-8.5	+	+	+	+	+	-	-	+	-	+	+
MPS Type VII	1	-/1	1.20	12.80	11.60	11.60	+	+	+	+	+	+	-	+	-	+	+
Mucolipidosis	3	F	0.5±0.61	4.33±4.17	2.22±3.17	0.6±4.4	+	+	+	+	+	+	-	+	-	+	+
α- Mannosidoses	2	-/2	1.5±0.35	11.12±9.36	9.62±9.72	3-16.4	+	+	+	+	+	+/-	-	+	-	+	+
Cystinosis	2	1/1	1.95±0.77	6.54±4.17	3.55±1.37	2.5-4.3	-	+	-	+	+	-	+	-	-	+	+

H - Hepatomegaly; S - Splenomegaly; C - Cardiac involvement; O - Osteoartropathy; R - Respiratory involvement; N - Neurogical impairment; RE - Renal impairment; HE - Hernia; HM - Hematological impairment; O - Ophtalmological impairment; HY - Hypoacusia

Mucopolysaccharidoses: All the 45 patients with different types of mucopolysaccharidoses presented coarse facial features, stiff joints, dysostosis multiplex, umbilical and inguinal hernias, hepatosplenomegaly in various degree and cardiac valve involvement. 28 patients with severe forms of MPS type I (two patients), MPS type II (17 patients), MPS type III (8 patients) and MPS type VII (one patient) presents variable grades neurological impairment consisted in speech delay, behavior problems, mild intellectual disability to dementia.

Mucolipidosis: in the three diagnosed patients, the symptoms, similar to those of mucopolysaccharidosis and sphingolipidosis, began early at the mean age of 0.5±0.61 years, with a mean age at diagnosis of 4.33±4.17 and an average delay of 2.22±3.17 years.

Alpha mannosidoses: The symptoms and signs appeared in both children at the age of one year, but the diagnosis was established at 4.6 and 17.75 years, respectively, with a delay of 3.5 years in the first case and 16.25 years in the second case.

Type II Glycogenosis (Pompe disease) – in case of the patient with infantile form of the disease, the diagnosis was established early, in contrast with the late-onset forms, when the diagnosis was established with an average delay of 6.5 ± 6.9 years (between 2.5 and 12.55 years).

In Cystinosis, the clinical onset was at 1.73 years (first patient) and 0.84 years (second patient) and the diagnosis was established at the age of at 5.14 years in the first case and at 3.2 years in the second case.

Discussion

The signs and symptoms in lysosomal diseases vary from disease to disease, symptoms occur because of an enzyme deficiency that inhibits the ability of the lysosomes present in each of the body's cells to perform their normal function. The clinical picture is progressively shaped as the accumulation of non-metabolized substrates in the body's cells and induce cellular, tissue and organ dysfunction [1]. Early clinical manifestations are nonspecific and similar to other common conditions, which leads to delayed establishment of the diagnosis [23]. Recognition of the associations of early nonspecific symptoms is very important and allows diagnosis in time, before the irreversible lesions produce. In severe forms of disease, where the enzyme activity is absent or very low, the symptomatology appears at a young age compared to attenuate forms, in which symptoms starts much later in childhood, adolescence or adulthood [8,18]. In type 1 non-neuropathic form of *Gaucher disease*, a mean age at clinical onset was 15.74±13.2 years (range 1 to 64 years), A mean delay of 14.59±14.3 years was noticed from clinical onset of symptoms to diagnosis, comparable data

were seen in other studies. Hematological manifestations, anemia and cutaneous hemorrhagic syndrome was seen in all patients. Hepatomegaly was present in all patients and splenomegaly in 62 patients, 27 underwent splenectomy. The bone disease was treated by orthopedic surgeons. *In mucopolysaccharidosis*, the clinical feature of the disease is outlined around the age of 18-24 months, but the first signs of the disease appeared in the first months of life. Although all types of MPS patients presented umbilical and/or inguinal hernia, upper respiratory tract infections, repeated catarrhal otitis from the first months of life, only in two cases the diagnosis was established before the age of one year. All the others had at the time of diagnosis coarse facial features, hepatosplenomegaly, joint stiffness, dysostosis multiplex, cardiac valvopathy in varies degrees. In most patients with *Fabry disease* the diagnosis was established late after decades of evolution, only after the appearance of major complications of the disease, stroke, heart attack at young age or chronic kidney disease / hemodialysis. Only in two children from affected families the diagnosis was established early before the onset of irreversible complications at 11 and 14 years, respectively.

Conclusions

The lysosomal storage diseases are rare or ultra-rare diseases with childhood onset, but these early signs and symptoms can lead to misdiagnosis, because these features are similar to other common causes. Most often the diagnostic is delayed, only when irreversible lesions occur and the vital organs damage do they become manifest. The specific treatment has become available for more and more lysosomal diseases, but early diagnosis is essential for a good clinical outcome.

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