Late-Onset Pompe Disease in a Patient with Cerebellar Hemorrhage

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Abstract

Pompe disease (glycogen storage disease type II) is a rare autosomal recessive multisystem disorder characterized by the deposition of glycogen in skeletal muscles and internal organs. The late-onset form is characterized by slow progression with proximal muscle damage, respiratory failure, and less severe internal organ damage than the infantile form.

The article presents a case report of a 61-year-old female patient who underwent inpatient treatment. The patient had been having progressive muscle weakness for over 20 years and had a positive family history, but the reason for further evaluation and treatment was hemorrhage in the left cerebellar hemisphere. Laboratory and instrumental data are presented and clinical manifestations are discussed.

Keywords: *Pompe disease; glycogen storage disease type II; cerebellar hemorrhage; dilated cerebral arteriopathy; diaphragmatic ultrasound; magnetic resonance imaging of the thigh soft tissues*

Ethical statement. The publication of the clinical case was carried out with the voluntary informed consent of the patient.

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Болезнь Помпе с поздним началом у пациентки с кровоизлиянием в мозжечок

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Аннотация

Болезнь Помпе (гликогеноз II типа) – редкое аутосомно-рецессивное мультисистемное заболевание, для которого характерно отложение гликогена в скелетных мышцах и внутренних органах. Поздний дебют заболевания характеризуется медленным прогрессированием с поражением проксимальной мускулатуры, явлениями дыхательной недостаточности и менее выраженным, чем при инфантильной форме, поражением внутренних органов.

В статье представлено клиническое наблюдение пациентки 61 года, проходившей стационарное лечение. У неё на протяжении более 20 лет наблюдалась прогрессирующая мышечная слабость, выявлялся отягощённый наследственный анамнез, однако поводом для обследования и лечения стало развитие кровоизлияния в левую гемисферу мозжечка. Приведены данные лабораторно-инструментальных методов обследования, обсуждены особенности клинических проявлений.

Ключевые слова: *болезнь Помпе; гликогеноз II типа; кровоизлияние в мозжечок; дилатационная церебральная артериопатия; ультразвуковое исследование диафрагмы; магнитно-резонансная томография мягких тканей бёдер*

Этическое утверждение. Получено добровольное информированное согласие пациентки на публикацию клинического случая.

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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Introduction

Pompe disease (glycogen storage disease type II; PD) is a rare autosomal recessive disorder characterized by the glycogen accumulation in the lysosomes of various tissues. This disease is caused by mutations in the *GAA* gene (OMIM #606800) located on the long arm of chromosome 17 (17q25.2-25.3) and encoding acidic α-1,4-glucosidase, an enzyme involved in the breakdown of glycogen in cellular lysosomes [1, 2]. PD is a multisystem disease. Although skeletal muscle damage is the predominant clinical manifestation, glycogen metabolism disorders are also observed in cardiac muscle, liver, smooth muscle, and other organs and tissues [2, 3].

The clinical picture of PD depends on the age of onset, with earlier onset predisposing to more severe disease. This can be explained biochemically by the persistent residual activity of acid alpha-1,4-glucosidase in late-onset patients [4, 5].

PD is divided into infantile and late-onset forms. The infantile form is more severe due to the extremely low (<1%) activity of alpha-1,4-glucosidase. Symptoms develop at birth or in the first few months of life. This form is characterized by severe hypotonia (floppy infant syndrome), rapidly progressive myopathy with respiratory muscle dysfunction, hypertrophic cardiomyopathy, hepatomegaly, and a high risk of death [6, 7]. Some authors also identify a non-classical childhood-onset form. In this group of patients, clinical symptoms include delayed motor development, myopathic (predominantly proximal muscle damage) and diarrheal syndromes, respiratory failure due to respiratory muscle weakness and atrophy, elevated blood levels of creatine phosphokinase (CPK), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) [7].

Later-onset PD (after the age of 1 year) often develops in adulthood. Progressive weakness of the trunk and proximal muscles with predominant damage to the lower extremity muscles is observed. Respiratory failure occurs and progresses with damage to the diaphragm. Cardiomyopathy is less common. Clinical symptoms may include bulbar muscle damage manifested by tongue weakness with dysarthria and dysphagia, sleep apnea, cardiac arrhythmias, gastrointestinal dysfunction, lower urinary tract and anal sphincter involvement [5, 8–10]. Late-onset PD is characterized by a slowly progressive course. The patient's condition depends on the degree of damage to the skeletal muscles and internal organs.

Significant increases in CPK, lactate dehydrogenase, ALT, and AST levels are the most common laboratory changes. Electroneuromyography can confirm myopathy. Muscle biopsy is not always helpful in establishing the diagnosis because typical changes may not be present in a muscle biopsy sample [1, 11, 12].

If PD is suspected, determination of acid alpha-1,4-glucosidase activity in dried blood spots by tandem mass spectrometry is a gold standard diagnostic test, and if it is decreased, molecular genetic testing by direct *GAA* gene sequencing should be performed to identify different mutations [1, 6, 13].

Clinical case

Female patient A, 61 years old, underwent planned inpatient treatment in the Neurological Department of the I.I. Mechnikov North-Western State Medical University.

The patient presented with unsteady gait, skeletal muscle weakness, especially in the proximal limbs and back muscles, difficulty getting out of bed and standing up from a chair (using myopathic maneuvers), pain in the skeletal muscles when moving, and decreased voice volume.

She reported having the disease since the age of 20–30, when she first noticed weakness in her back muscles and difficulty maintaining an upright position. This was followed by a slow progression of the disease with abnormal gait and damage to the proximal muscle groups of the legs and arms. She did not seek medical attention for the above complaints.

The family history was clarified; the diagram is shown in Fig. 1. The patient's brother (deceased) had progressive muscle weakness since the age of 25, requiring respiratory support (artificial ventilation). The nephew (30 years old) had a 2–3 year history of slowly progressive skeletal muscle weakness. The nephew's son had progressive muscle weakness in early childhood, including respiratory muscles, requiring mechanical ventilation and resulting in death at the age of 4 years.

On the evening of 15 March 2024, the patient noticed a general deterioration, acute dizziness, a clicking sensation in her head followed by loss of consciousness, and a single episode of vomiting. She was urgently admitted to the Regional Vascular Center for further evaluation and was diagnosed with hemorrhagic stroke with intracerebral hematoma in

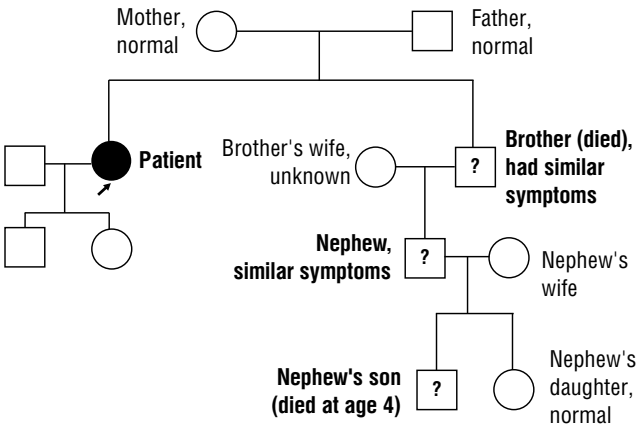

Fig. 1. Family history of patient A.

the left cerebellar hemisphere. She received neuroprotective and vascular therapy in the hospital. She was discharged for outpatient treatment in stable condition.

In April 2024, the patient was admitted to the Neurology Department No. 1 of the I.I. Mechnikov North-Western State Medical University with the status post hemorrhagic stroke with intracerebral hematoma in the left cerebellar hemisphere on 15 March 2024 with severe dynamic ataxia; early recovery period. During hospitalization, she received antiplatelet, lipid-lowering, hypotensive, neuroprotective, exercise and physical therapy, and biofeedback training. During the course of treatment, positive changes were observed with significant improvement in dynamic ataxia. Based on the identification of a hereditary myopathy and gait abnormalities not typical of a previous acute cerebrovascular event, it was recommended to perform additional examinations to rule out late-onset PD, such as alpha-1,4-glucosidase activity by dry spot assay and molecular genetic testing. It should be noted that there were no significantly elevated levels of CPK and other cytolytic enzymes according to the medical records provided.

On 5 November 2024 she was readmitted to Neurology Department No. 1 of the I.I. Mechnikov North-Western State Medical University. At admission, her condition was relatively satisfactory. She was alert and cooperative. The performance status was characterized by lower thoracic and lumbar S-shaped scoliosis. No abnormal changes in the cardiovascular, respiratory, digestive, or genitourinary systems were observed. Respiratory rate was 16 per minute; SpO_2 was 94%.

Sense of smell was not affected. Visual fields by the confrontational test were unrestricted. Eye-slits were D=S. Full range of eye movements was observed with no diplopia or pain. Pupils were OD=OS, light reflexes (direct and indirect) were brisk. The convergence and accommodation reflexes were reduced bilaterally. A horizontal fine end-point nystagmus was observed in the extreme positions. Facial sensitivity was not affected. The face was asymmetrical due to the reduction in the right nasolabial fold. The palpebral reflex was D=S and moderately brisk. The cochlear and vestibular systems were not affected. No dysphagia, dysarthria, dysphonia was observed. The tongue was in the midline. The soft palate was symmetrically tensed, and the uvula was in the midline. No primitive oral reflexes were revealed. The myopathic gait was observed with leaning on surrounding objects. The patient used Gowers' maneuvers to rise from the chair. Table 1 shows the results of strength testing of the major skeletal muscle groups using a Medical Research Council Scale for Muscle Strength (MRC-5). Moderate paresis of the shoulder and pelvic girdle muscles was noticed.

The range of active movements was restricted when lifting the arms above the horizontal position due to muscle weakness. The range of passive movements was normal. The muscle tone was diffusely reduced. Hypotrophy of the shoulder and pelvic girdle muscles was noticed, with winged scapulae (Fig. 2). No fasciculations or fibrillations were observed. Deep reflexes were as follows: equal and moderately brisk in the arms and uniformly reduced in the legs. As for pathological reflexes, the upper and lower Rossolimo reflexes were detected on the left side.

The finger-to-nose and finger-to-hammer tests were satisfactory bilaterally, while the heel-to-shin test showed bilateral ataxia, more severe on the left. The Romberg test showed unsteady gait without clear lateralization. Babinski asynergy test could not be reliably performed due to weakness of the back muscles. No dyshypermetry or dysdiadochokinesia was observed. The Stuart–Holmes test was negative. The patient presented with impaired surface sensitivity manifested as a mosaic pattern of the left-hand hypoesthesia. Deep sensitivity was intact. No signs of nerve root tension were detected.

No aphasic, apraxic, or agnosic disorders were observed. The Mini Mental State Examination (MMSE) score was 30. The Montreal Cognitive Assessment (MoCA) score was 28. The Frontal Assessment Battery (FAB) score was 18.

No meningeal signs were observed. Pelvic organ functions were intact.

The Hospital Anxiety and Depression Scale (HADS) showed an anxiety score of 2 and a depression score of 11. The patient was consulted by a psychotherapist. The depression subscale score identified was associated with a chronic, slowly progressive disease.

The patient's forced vital capacity (FVC) was 37% of the normal value adjusted for sex, height, and age in the sitting position and 29% of the normal value in the supine position.

The 6-minute walk test result was 318 meters.

Follow-up laboratory testing for myolysis showed a slight increase in lactate dehydrogenase level (235 U/L; reference range: 79–221 U/L), while the CPK level was 93 U/L and remained within the reference range of 26–174 U/L.

The patient's brain natriuretic peptide level was 118.6 pg/mL, which was below the reference range (300–900 pg/mL for subjects aged 50–75 years).

Abdominal ultrasound did not show any liver abnormalities, but revealed a gallbladder polyp. A decrease in the range

Table 1. Results of muscle strength testing in patient A.

Movement	Right	Left
Forward neck flexion	4	4
Backward neck flexion	4	4
Lifting arms to the horizontal position	3	3
Lifting arms above the horizontal position	2	2
External shoulder rotation	3	3
Internal shoulder rotation	3	3
Elbow flexion	4	4
Elbow extension	4	4
Forearm supination	4	4
Forearm pronation	4	4
Hand flexion	4	4
Hand extension	4	4
Finger flexion	5	5
Finger extension	5	5
Finger abduction	5	5
Finger adduction	5	5
Hip flexion	3	3
Hip extension	3–4	3–4
Hip adduction	4	4
Hip abduction	4	4
External hip rotation	4	4
Internal hip rotation	4	4
Knee flexion	4	4
Knee extension	4	4
Foot dorsiflexion	4–5	4–5
Foot plantar flexion	5	5
Foot abduction	5	5
Foot adduction	5	5
Toe extension	5	5
Toe flexion	5	5

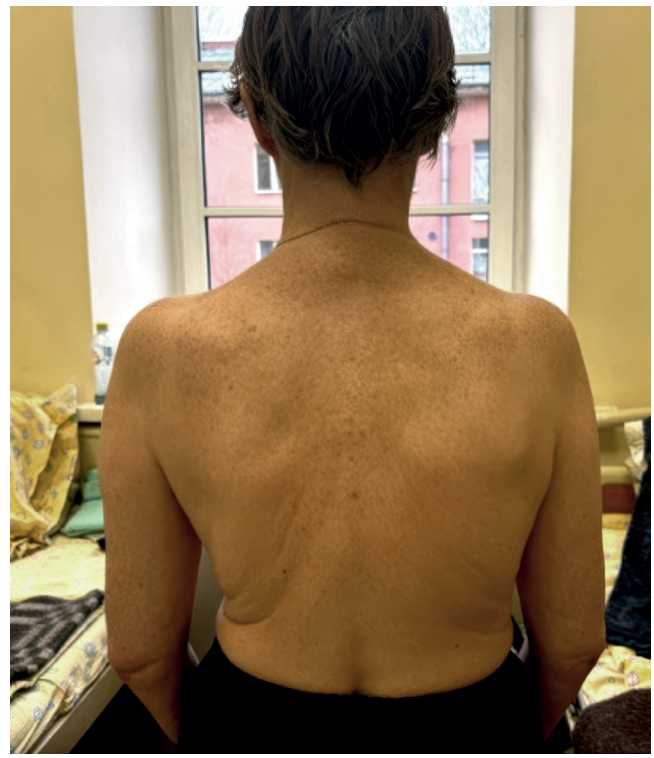

Fig. 2. Atrophy of the shoulder girdle muscles in Patient A, with signs of developing winged scapulae.

of movement to 7 mm for the right hemidiaphragm and to 10 mm for the left hemidiaphragm was noticed (reference range: 10–20 mm).

A diaphragmatic ultrasound was performed using 5–12 MHz sensors in B and M modes in the standing, semi-recumbent, and supine positions with an assessment of diaphragm thickness and excursion. At least 3 measurements were taken for each parameter, and the average value was calculated.

Tables 2 and 3 show the numerical parameters of the diaphragmatic ultrasound. All tested parameters were below reference ranges.

Triplex scanning of the brachiocephalic arteries showed dilation and curvature of the brachiocephalic trunk, subclavian arteries, S-shaped tortuosity of the common carotid arteries, tortuosity of the middle and distal segments of the internal carotid arteries, and VI segment of the vertebral arteries without evidence of significant stenosis. A prolonged heteroechoic atherosclerotic plaque with hyperechoic inclusions and a nodular outline was observed along the inferior wall of the right subclavian artery, stenosing the lumen by up to 44%. No evidence of subclavian (vertebral) steal syndrome was seen. Hypoplasia of the left vertebral artery could not be ruled out.

Previously recommended additional tests are presented. Dry spot assay of alpha-1,4-glucosidase activity showed a low level of 1.3 μmol/L/h (reference: > 2.32 μmol/L/h). Molecular

Table 2. Diaphragm thickness (mm) in patient A. according to ultrasound

Time of the examination	Position	Parameter			
		right		left	
		result	reference range	result	reference range
End-expiratory	Supine	1.1	1.7–2.2	1.1	1.7–2.2
	Semi-recumbent	1.2		1.1	
	Standing	1.4		1.4	
End-inspiration	Supine	1.4	1.9–2.7	1.4	2.0–2.8
	Semi-recumbent	1.4		1.5	
	Standing	1.5		1.6	
End of full inspiration	Supine	2.1	2.6–3.5	2.1	2.8–3.9
	Semi-recumbent	2.1		2.2	
	Standing	2.7		2.7	

Table 3. Range of diaphragm movements (mm) in patient A. according to ultrasound

Parameter	Position	Results	Reference range
Normal breathing	Standing	7.1	11.1–16.9
	Lying	6.5	
Deep breathing	Standing	27.6	39.3–63.6
	Lying	26.5	

genetic testing showed a pathogenic nucleotide variant chr17:80112604G>A in the heterozygous state and a likely pathogenic nucleotide variant chr17:80112993C>G in the heterozygous state in *GAA*.

The patient was referred to magnetic resonance imaging (MRI) of the soft tissues of the right and left thighs. Symmetrical fatty degeneration of the muscles of the posterior thigh compartment (semimembranosus, semitendinosus, biceps) and large adductor muscles of the thigh was observed with no signs of edema, involvement of fat tissue, fascial compartments, and vascular-nervous bundles (Fig. 3).

Severe symmetrical fatty degeneration of the posterior muscles of the thigh (black arrow) and moderate fatty degeneration of the adductor muscles of the thigh (white arrow) are visualized.

Based on clinical, laboratory, instrumental, and molecular genetic tests, the patient was diagnosed with late-onset progressive glycogenosis type II with myopathy of the proximal extremities and trunk, moderate hypotrophy, and moderate respiratory dysfunction.

The patient received previously prescribed antiplatelet, antihypertensive, and neuroprotective therapy. The subsequent management strategy included enzyme replacement therapy.

Discussion

Timely diagnosis of late-onset PD is challenging in most cases. When a patient first presents to a neurologist with a "typical" course of late-onset PD and data on complaints, history, and neurological status are obtained, myodystrophies, polymyositis, spinal amyotrophy, and myasthenic syndrome should be differentiated. However, patients adapt to the slowly progressive muscle weakness and atrophy, and clinical manifestations of damage to other organs may be the first complaint to seek medical attention from various specialists, such as pulmonologists, rheumatologists, orthopedic surgeons, gastroenterologists, etc. [2, 12, 14].

Late diagnosis, in turn, complicates patient management by delaying the initiation of pathogenetic therapy.

In our clinical case, patient A had been having progressive muscle weakness and atrophy for almost 30 years, but the reason for consulting a neurologist was a parenchymal hemorrhage in the left cerebellar hemisphere. Stroke is reported as one of the rare complications of PD. Stroke pathogenesis in this group of patients is caused by abnormal accumulation of lysosomal glycogen in the smooth muscle cells of brain arterioles and arteries, which affects the synthesis and structure of the extracellular matrix and reduces the elasticity and integrity of the vessel wall. In addition, the vertebrobasilar arteries are more vulnerable due to the lower expression of elastic fibers in their walls compared to the carotid arteries. These changes result in dilated arteriopathy, dolichoectasia of the basilar artery, and microaneurysms. This increases the risk of parenchymal hemorrhage into the brain matter (as in patient A), subarachnoid hemorrhage and microbleeds, as well as cerebral infarction and leukoencephalopathy. In addition, an increase in partial pressure of carbon dioxide as respiratory failure progresses may be a risk factor for vasodilation in patients with PD [15]. In our case, duplex scanning also showed multiple tortuosities of the brachiocephalic arteries, confirming the literature data. However, the parenchymal hemorrhage in the left cerebellar hemisphere was accompanied by a significant improvement in focal symptoms during the treatment.

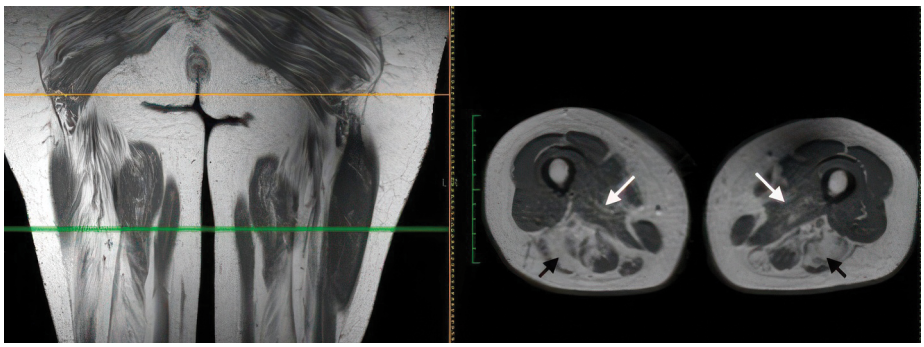

Fig. 3. Results of MRI of soft tissues of the thighs of patient A. (T1-weighted, frontal and axial slices).

During the hospitalization in the Neurology Department, which is the main base of the Department of neurology named after academician S.N. Davidenkov of the I.I. Mechnikov North-Western State Medical University, clinical manifestations of the patient's long-term neuromuscular disease were the focus of attention. The relevant medical history revealed the hereditary nature of the disease. Additional clinical and laboratory tests ruled out non-hereditary variants (inflammatory, toxic, endocrine, tumor-induced) of progressive muscle damage.

Analysis of the family history suggested a hereditary nature of the disease, but the mode of disease transmission was not typical of PD, as it appeared to be an autosomal dominant inheritance. However, autosomal recessive PD was not confirmed in deceased relatives (the patient's brother, the son of the nephew). Such a pseudodominant inheritance was only possible if the wives of the patient's brother and nephew were carriers of the mutation. Considering the low incidence of heterozygous carriers of *GAA* mutations, the probability of such a case is extremely low. Autosomal recessive inheritance is characterized by cases of disease in relatives of both sexes in different generations. Therefore, the family history was not typical of PD.

Moreover, the diagnosis in this case was challenging due to the lack of typical laboratory markers of myolysis in follow-up blood chemistry results, whereas in the majority of clinical cases described in the literature, hyper-creatine phosphokinase-emia was found [9, 16, 17]. Enzyme levels within the reference range may be associated with a long, slowly progressive disease (over 20 years) with severe chronic muscle damage [18].

In our case, the diagnosis was verified by measuring alpha-1,4-glucosidase activity in dried blood spots using tandem mass spectrometry, followed by molecular genetic testing. The patient had compound heterozygous mutations in the *GAA* alleles (pathogenic nucleotide variant chr17:80112604G>A and likely pathogenic nucleotide variant chr17:80112993C>G), which may explain the late onset of the disease with enzyme levels within the reference range. Currently, genotype-phenotype correlations in PD patients are of great interest because genetic and epigenetic mechanisms of the disease's clinical polymorphism are not fully understood.

We believe that assessment of respiratory muscle function is an important element of the evaluation of patients with neuromuscular disorders. FVC in the vertical and horizontal positions is the simplest and most commonly used clinical test to detect diaphragmatic paresis. In our case, FVC decreased to 37% of reference in the vertical position and to 29% in the horizontal position. The literature provides some data on the correlation between FVC and respiratory morbidity and mortality [11, 12, 15]. In our case, we used diaphragmatic ultrasound, which showed a decrease in diaphragm thickness and excursion below the reference ranges. In the available Russian literature, despite the simple and informative nature of ultrasound, we found no cases of diaphragmatic ultrasound in PD patients. Global literature describes only a few cases of diaphragmatic ultrasound [19].

The thigh muscle MRI of our patient showed a significantly more severe fatty degeneration of the posterior thigh muscles compared to the medial ones, which can be considered as an individual feature.

Current clinical guidelines [20] recommend watchful waiting for patients with PD, including monitoring of FVC, regular 6-minute walk tests, liver ultrasound, electrocardiography, echocardiography, follow-up measurement of myoglobin fraction of CPK, and brain natriuretic peptide.

The treatment strategy for PD patients involves a multidisciplinary approach based on the clinical manifestations of the disease. Recommended non-medication options include a high-protein, low-carbohydrate diet supplemented with L-alanine, psychotherapeutic support, and psychological adjustment. Lifelong enzyme replacement therapy is the primary pathogenetic treatment option used to slow disease progression, stabilize lung function, and prolong patients' lives before they require ventilatory support and a wheelchair.

Conclusions

Therefore, clinical diagnosis of late-onset PD may be significantly challenged. If myopathic syndrome is suspected in patients seen by different specialists for different diagnoses, additional testing, including FVC, is recommended. We believe that diaphragmatic ultrasound has great potential as a diagnostic tool for patients with PD and other neuromuscular disorders due to its availability, informative value, and non-invasiveness.

All patients with unspecified limb girdle myopathy, especially if associated with respiratory muscle weakness, should have a blood test for alpha-1,4-glucosidase activity. It should

be considered that family history is not always available and that elevated CPK and other markers of myolysis are not necessarily indicative.

The accumulation of lysosomal glycogen in the smooth muscle cells of brain arterioles and arteries, with associated structural alterations in the intercellular substance, is a risk factor for dilated arteriopathy, which increases the risk of stroke and leukoencephalopathy. Neurologists' awareness of cerebrovascular PD manifestations is the only way to suspect and diagnose this disease.

PD is a curable disease with pathogenetic treatment available, so early diagnosis and timely initiation of therapy are crucial. Pathogenetic treatment of PD appears to be the most optimal treatment strategy to prevent cerebrovascular complications, but the current scientific literature does not provide relevant data, so further research is needed.

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