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Non-muscle involvement in late-onset Glycogenosis II

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Glycogenosis II (GSD II) is an autosomal recessive lysosomal storage disorder resulting from acid alpha-glucosidase deficiency, subsequent accumulation of glycogen in tissues, impairment of autophagic processes and progressive cardiac, motor and respiratory failure.

The late-onset form is characterized by wide variability in residual enzyme activity, age of onset, rate of disease progression and phenotypical spectrum. Although the pathological process mainly affects the skeletal muscle, several other tissues may be involved in the course of the disease; therefore GSD II should be regarded as a multisystem disorder in which glycogen accumulation is present in skeletal and smooth muscle, heart, brain, liver, spleen, salivary glands, kidney and blood vessels.

In this review, we briefly summarize the main non-muscle targets of the pathological process in late-onset GSD II.

Further studies aimed at evaluating the extra-muscle involvement in this group of patients will help to better define clinical features and prognostic factors and to delineate the natural history of the disease.

Key words: Glycogenosis II, GSDII, Pompe disease

Glycogenosis II (GSD II; Pompe's disease; OMIM entry # 232300) is a storage disorder resulting from a deficiency of acid alpha-glucosidase, which is the only enzyme able to process glycogen into lysosomes. Enzyme deficiency leads to accumulation of glycogen in muscles, lysosomal disruption and excess of autophagic vesicle buildup inside the myofibers, causing progressive cardiac, motor and respiratory failure (1).

GSD II can be clinically divided into two main subtypes. The infantile form usually appears in the first month of life, presents with severe cardiac involvement and total deficiency of alpha-glucosidase activity (< 1% of normal controls), and progresses rapidly; the late-onset form is characterized by phenotypical variability even though the main findings are progressive muscle weakness and severe respiratory insufficiency (2, 3).

Limb-girdle weakness is frequently the early sign of the late-onset disease. Patients usually report difficulty in walking and running, playing sports, climbing stairs or rising from a chair. Severe weakness may also be observed in paraspinal muscles and additional neuromuscular features may include scapular winging and distal contractures. Respiratory muscles are always involved with weakness of the diaphragm, intercostal and accessory muscles whereas the cardiac damage is usually less severe (2). Muscle weakness and limited movement, especially of the antigravity muscles, may lead to alterations of posture, severe scoliosis and lumbar hyperlordosis, which entail biomechanical disadvantages, muscle contractures and deformity in a vicious circle of progressive disability.

Increasing evidence shows that systemic abnormalities are present in GSDII patients and several tissues other than muscles may be involved in the course of the disease; therefore GSD II should be regarded as a multisystem disorder in which glycogen accumulation is present in skeletal and smooth muscle, heart, liver, kidney, spleen, salivary glands, glial cells, brainstem nuclei, anterior horn cells of spinal cord and blood vessels (2).

In this review we briefly summarize the non-skeletal muscle targets of the pathological process in late-onset GSD II.

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Nervous system involvement

In Pompe mice, mass spectrometric quantification showed that glycogen progressively accumulates in brain (4). In pathological studies, glycogen storage was detected in cell bodies throughout the gray matter of the spinal cord, in cerebrum and cerebellum neurons, in glial and Schwann cells (5).

Interestingly, animal models clearly showed glycogen accumulation in spinal and medullary respiratory neurons (6, 7). Glycogen storage was especially noted in phrenic motoneurons which also had larger soma area compared with wild-type controls (6). These findings may indicate a damage of the neural output to the diaphragm with impairment in the neural control of breathing which could contribute to the respiratory dysfunction (6, 7).

In humans, glycogen storage was repeatedly reported in nervous system of infant patients. Similarly to animal models, accumulations are located in the gray matter (neurons of the anterior horns of the spinal cord and brainstem and cortical neurons of the brain and cerebellum) (6, 8-10) as well as in oligodendrocytes with delay in myelination as early as the second trimester of gestation (11-13). Neuronal loss with areas of gliosis both in brain and spinal cord was also described (10). In the peripheral nerves, Schwann cells with glycogen-filled projections which may interfere with the correct formation of myelin was observed (13). From a clinical point of view, a variable degree of cognitive development was reported in infant patients (14). During the first 4 years of life, cognitive developmental scores in 10 children ranged from above-average development to developmental delay with mild mental retardation and brain imaging revealed periventricular white matter abnormalities in 4 of them (14).

Differently from the infantile form of the disease, nervous system involvement in late-onset GSD II patients was poorly studied.

The autopsy findings in a clinically and biochemically documented case of adult-onset disease showed no significant morphological abnormalities in the nervous system (15).

Recently, brain structure and function in adult GSD II subjects were evaluated by Voxel-based morphometry (VBM), an MR technique to assess structural gray matter modifications, and by resting state functional MRI (fMRI), which is a method able to provide measures of functional brain connectivity (evaluation of interrelations between different brain regions that are part of common networks subserving complex brain functions) (11). Neuroimaging and neuropsychological findings showed significant changes in brain connectivity of the explored functional brain networks. Particularly, the Wisconsin card sorting test, which is able to detect dysfunctions of the frontal lobe, showed impaired performance in set shifting abilities, cognitive flexibility and problem solving. Functional neuroimaging showed a selective disruption of the Salience Network, implicated in executive functioning, planning and abstract reasoning, which is consistent with the findings of the neuropsychological profile. Differently, VBM analysis did not reveal any significant regional brain atrophy in line with autopsy studies that did not report any evidence of cortical atrophy (11, 15), thus suggesting functional disruption of neuronal networks without macroscopic structural changes in GSD II adult brains.

Blood vessel involvement

Brain vascular abnormalities were reported in late-onset GSD II. They include basilar artery dolichoectasia, internal carotid dilative arteriopathy and aneurysms of basilar, internal carotid or cerebralis media arteries and can be a serious complication of late-onset cases by provoking bleeding that leads to severe neurologic deficits or death (16, 17). Studies of prevalence suggest that they are more common in patients with late-onset GSD II than in general population (16, 17). Some of the reported patients had neurological signs and/or symptoms directly related to cerebrovascular abnormalities, such as transient ischemic attacks and neurovascular conflicts resulting in cranial nerve involvement (16, 17). Rarely vascular abnormalities were described in different areas than the brain, such as aneurysms of the left ventricle of the heart (18).

Vacuolar degeneration and glycogen deposits were found in the vessel walls and in smooth muscle cells of cerebral arteries and other blood vessels (15). The progressive loss of integrity of these structures over the course of disease may explain the occurrence of dilatative arteriopathies or aneurysms in these patients (16).

There is a recent report of a late-onset GSD II patient with an intramuscular hemangioma located in the right semimembranosus muscle (19). Intramuscular hemangiomas are quite rare abnormalities and make up 0.8% of all hemangiomas (19). Although a coincidental occurrence can be not completely ruled out, the rarity of muscle hemangiomas in the general population as well as the propensity of GSDII patients to have vascular abnormalities should induce to evaluate also the peripheral vascular axes in the diagnostic process and follow-up of these subjects.

Bone involvement

A high frequency of vertebral and femur fractures was reported in infants and osteopenia was described in long-term survivors with infantile GSD II (2, 20-22).

At present, not many studies on bone metabolism in late-onset GSD II are available (2).

However, there is no doubt that bone involvement is an under-recognized issue in this group of patients. Bone mineral density is significantly lower in GSD II patients than in healthy individuals and osteoporosis is present in both wheelchair-bound and ambulant patients (2, 23, unpublished personal observation). Oktenli described an adult patient who presented with low bone density and vertebral fragility associated with hypocalcaemia, hypocalciuria and renal magnesium wasting due to the accumulation of glycogen in distal tubules (24).

Even though loss of muscle function and limited movement can contribute to loss of mineral content, development of osteopenia and a higher risk of fracture (2, 23, 24), further studies are mandatory in order to explore the role of possible primary bone metabolism dysfunctions in the pathogenesis of bone alterations in this group of patients.

Other features

Fatigue is a frequent complaint of GSD II patients, it is characterized by difficulty in initiating and sustaining voluntary effort and is not related to age, sex or disease duration (25). The Fatigue Severity Scale (FSS) was assessed in an international population of 225 adults with GSDII and the mean FSS score was significantly higher than that of healthy controls (25). Respiratory insufficiency and subsequent fragmented sleep can be possible causes but central or peripheral mechanisms have also been suggested (25).

Hearing loss was reported in late-onset GSD II (26). Evaluation of the auditory system by speech and pure tone audiometry, impedance audiometry and auditory brainstem responses showed subclinical sensorineural deficits, conductive hearing loss or mixed patterns in most of the patients studied, thus confirming that hearing impairment is more frequently present than previously thought (26).

Sleep-disordered breathing, for instance the occurrence of central, obstructive or mixed apnea and/or hypoventilation during sleep, may be present in GSD II subjects (27). Over time, sleep related hypoventilation may become more prolonged and promote severe hypoxia and depression of the respiratory drive. This results in stable nocturnal and diurnal hypoventilation, right ventricular strain and acute cardiopulmonary failure (2,27). Obstructive events during sleep that cause obstructive sleep apnea have also been reported, which can be due to upper airway collapse caused by pharyngeal or laryngeal muscle weakness, obesity being an unfavourable concomitant factor in some patients (27-29).

Constipation and other gastrointestinal symptoms were reported in patients with GAA deficiency and are likely related to accumulation of glycogen in the smooth muscle of the gastrointestinal tract or in ganglion cells of Meissner's and Auerbach's plexus with subsequent impairment of bowel motility (5, 16).

Recently, a study of metabolism and methylation capacity was conducted in patients with late-onset GSD II by biochemical analyses of blood and urine in order to evaluate the citric acid cycle, methylation capacity and nutrient sensor interaction (30). Patients had a disturbed energy metabolism, a diminished plasma methylation capacity and a higher levels of insulin-like growth factor type 1 and its carrier (protein insulin-like growth factor binding protein 3), thus exhibiting a nutrient sensor disturbance with secondary energy failure leading to a chronic catabolic state (30).

Conclusions

Although muscle is the mainly involved tissue, other tissues may be affected by the disease process. At present, only few studies on non-muscle tissue involvement in late-onset GSD II are available. Further research aimed at evaluating GSD II from "the viewpoint of a multisystem disease" is needed in order to better define clinical features and prognostic factors and delineate the natural history of the disease.

The evidence of a multisystem involvement opens up new therapeutic challenges. The prolonged survival expected with the enzyme replacement therapy could lead to more evident clinical manifestations of non-muscle tissue damage.

Especially central nervous system involvement deserves attention because the recombinant enzyme currently used in treating GSD II does not cross the blood brain barrier and cannot effectively counteract the central nervous system damage (12, 31).

The ability of new therapeutic options to reverse or lessen the degree of central nervous system dysfunctions should be a focus of future investigations.

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