Spontaneous Hydromyelic Cavity in Two Unrelated Patients with Late-Onset Pompe Disease: Is This a Fortuitous Association?

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Dear Sir,

Late-onset Pompe disease (LOPD) is an autosomal recessive lysosomal storage disease due to glucosidase alpha acid (GAA) deficiency leading to intracytoplasmic glycogen accumulation [1]. Prevalence of LOPD varies in populations at between 1:40,000 and 1:146,000 [2].

Hydromyelia is a dilatation of the spinal central canal which communicates with the intracranial cerebrospinal fluid compartment [3, 4]. It can lead to neurologic deficits including in some cases muscle weakness and atrophy [3, 5]. Hydromyelia is considered a rare condition [6], but its exact incidence seems unknown.

Syringomyelia arises primarily outside the central canal and secondary to Chiari malformation, tumor, traumatism or bleeding [4, 5]. Its incidence is estimated at around 8.4 new cases/year/100,000 people [7].

In some cases, hydromyelia is considered a 'pre-syringomyelic' stage or a pre-disposition to syringomyelia [8, 9].

We report for the first time, 2 cases of association between hydromyelic cavity

(fortuitously found) and LOPD. We present clinical history and imaging. We discuss possible pathophysiological explanations and clinical implications.

Patients and Methods

In a previous study on LOPD [10], we discovered 2 patients (n = 39) (P20 and P34) with hydromyelia. We carefully assessed them clinically and performed a review of the literature.

A summary of the clinical data and ancillary tests is shown in table 1.

Patient 1

A 56-year-old male patient was investigated for progressive limb weakness over the previous 3 years. Past medical and family history was unremarkable. Neurologic examination revealed a proximal quite symmetric weakness [Medical Research Council (MRC) score 3–4/5], without sensory disturbances or pyramidal signs. Because no etiologies were found to explain

the progressive tetraparesis, in order to exclude a spinal cord disease, spine magnetic resonance imaging (MRI) was performed and showed a Th6–Th8 hydromyelia (fig. 1). Later, a high creatine kinase (CK) level (threefold upper normal value) and pathologic electromyography (EMG) indicated muscle disease. Muscle biopsy showed an enhanced acid phosphatase stain that is suggestive for lysosomal activation as seen in Pompe disease. Low levels of alpha acid glucosidase activity were measured in leukocytes as well as in the muscle (26.80 and 6.05%).

The patient carried two pathogenic mutations on the GAA gene (c.-32–13T>G and c.2481 + 102_2646 + 31del).

Patient 2

A 51-year-old male patient had developed progressive muscle weakness and dyspnea over the previous 5 years. Past medical and family history was unremarkable except for a head injury 13 years earlier without any after effects. Neurologic examination disclosed proximal symmet-

Table 1. Main clinical findings and ancillary test results

	Patient 1	Patient 2
Sex	male	male
Age at first symptoms	53	46
Age at discovery of hydromyelic cavity	56	55
Age at assessment	64	66
Initial phenotype	limb weakness and exercise intolerance	limb weakness and respiratory distress
Neurologic examination at diagnosis time	axial and four limb weakness and decreased reflexes	axial weakness, facial weakness and decreased reflexes
Sensory disturbances	none	none
Walton scale (/10)	2	3
Pelvic modified MRC score, %	70.8	86.7
Mean global modified MRC sum score, %	85.4	94.8
Scoliosis	no	yes
Respiratory assistance	no	noninvasive nocturnal ventilation
Spirometry (seated)	restrictive	restrictive and obstructive
FVC (most recent and upright), % of predicted value	79	64
CK level, × upper normal value	3	3
EMG pattern	mixed	myogenic
Muscle biopsy findings		
Fiber size variability	++	–
Vacuoles	–	–
Acid phosphatase stain	++	+++++
Leukocyte alpha acid glucosidase assay, % of mean control activity	26.80	28.12
Muscle alpha acid glucosidase assay, % of mean control activity	6.05	3.29
Genetic (second mutation, both disclosing: c.-32–13T>G on one allele)	c.2481+102_2646+31del	c.525delT

FVC = Forced vital capacity.

Fig. 1. Spine MRI of patient 1 shows dilatation of the central canal regarding vertebrae Th6–Th8. Because it is limited to central canal dilatation, it argues for a diagnosis of hydromyelia. **a** Sagittal T2 MRI imaging. **b, c** Axial T2 MRI imaging. Arrows show the hydromyelic cavity.

ric weakness (MRC score 3–4/5), without sensory disturbances or pyramidal signs. Four years later, he presented subacute respiratory insufficiency. The patient underwent spine MRI to exclude spinal cord disease that revealed two centromedullary dilations (cervical C5–C7 and thoracic Th5–Th6).

The CK level was increased to threefold the upper normal value and EMG showed a myogenic pattern. The muscle biopsy also showed an important increase of acid phosphatase stain. Low levels of alpha acid glucosidase activity were found in leukocytes as well as in the muscle (28.12 and 3.29%). The patient carried two pathogenic mutations on the GAA gene (c.-32–13T>G and c.525delT).

Neither patient had underlying causes for hydro(syringo)myelia such as neoplasm, infection or spine traumatism.

Discussion

Without prospective explorations, in our small LOPD cohort (n = 39), we found 2 patients with hydromyelia. The exact frequency of hydromyelia in the general population does not seem to be precisely known but its occurrence in 2 patients in our small population could not simply be due to chance.

Spine MRIs were performed because of the tetraparesis and neither of these 2 patients had a previously described cause of hydro(syringo)myelia. Because of the lack of underlying pathology, the absence of specific symptoms (especially sensory) and the MRI findings, we considered a diagnosis of hydromyelia (instead of syringomyelia).

Patient 2 had had a head injury 13 years before the spine MRI. Spine trauma is de-

scribed as a possible cause of syringomyelia [5], whereas to the best of our knowledge, head injury is not.

The minimal prevalence of 5% of hydromyelia in our sample suggests an overrepresentation of this rare condition [6] in LOPD patients compared to the general population (rare disease being defined as a prevalence lower than 0.05%).

Glycogen storage disease type II is a multisystemic disorder: murine models [11] and human studies [12, 13] have shown that in Pompe disease, glycogen accumulation reaches almost all tissues including the central nervous system.

The association between these two rare entities could not be entirely due to chance. ‘Arachnopathy’ is a well-described cause of hydro(syringo)myelia that could be related to disturbances of the cerebrospinal fluid hydrodynamics and/or related to vascular obstructions [5, 14–16]. Because pathological studies demonstrated, in Pompe disease, intravascular (arteries and veins) glycogen accumulation [11], local spinal circulating failure due to glycogen accumulation in the walls of the blood vessels could be involved as a potential pathophysiological mechanism leading to the development of syrinx. This phenomenon could explain a defect of fluid transportation along the perivascular spaces that have been involved in the pathophysiology of syrinx development [16]. Moreover, blood circulation failure has been previously described as being involved in the formation of hydromyelia [14, 15].

Several Pompe-focused pathological studies showed spinal neural and non-neural cell loss [11, 12, 17]. Because Whener et al. [14] propose the hypothesis that spine tissue loss secondary to necrosis could lead to hydromyelia, we think that the loss of

spinal cells observed in Pompe disease could also be involved in the pathophysiology of hydromyelia in our patients [18]. We cannot exclude the hypothesis that a combination of these mechanisms and perhaps other hypotheses could be involved when trying to explain this association (e.g. a diminished thoraco-abdominal pressure related to the muscle weakness that could disturb the cranospinal pressure balance with an increased spinal cerebrospinal fluid pressure as seen in the immediate post-cough period [16]).

In the future, if the role of these mechanisms is confirmed on animal models or in humans, it could contribute to the understanding of the still controversial process leading to hydro(syringo)myelic cavity formation.

If future research confirms this association, its identification could have clinical implications.

Awareness of the presence of a hydro(syringo)myelic cavity in LOPD patients could be important because its symptoms, such as musculoskeletal ache, cramps, muscle weakness and atrophy, respiratory insufficiency (sometimes acute) or kyphoscoliosis, can overlap those that are due to muscle disease progression [5, 8, 18, 19] (or the failure of enzyme replacement therapy). A distinction must be drawn between the two conditions in order to provide the appropriate care.

Prospective systematic spine MRI assessment for hydro(syringo)myelia in LOPD could be an interesting subject for future research.

Disclosure Statement

None.

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