LATE ONSET POMPE DISEASE (LOPD) IS A MULTISYSTEMIC DISORDER: CENTRAL NERVOUS SYSTEM INVOLVEMENT

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INTRODUCTION

Pompe disease is a rare metabolic disorder due to acid alpha-glucosidase (GAA) deficiency. Its impairment leads to glycogen accumulation in multiple tissues with a predilection of skeletal muscle, heart and smooth muscle. Clinical presentation of Late-Onset Pompe Disease (LOPD) is usually characterized by a proximal/axial muscle weakness, often associated with respiratory impairment or by presymptomatic hyperCKemia with aches and fatigability. Nevertheless, Pompe disease may be considered as a multi-systemic disorder since many reports have demonstrated large involvement of other tissues and organs. In fact, recently, some reports documented the presence of cerebrovascular malformations in LOPD patients, likely due to glycogen accumulation in blood vessel walls[1,2]. In a previous study we demonstrated that a lacunar encephalopathy detected by brain CT well correlated with respiratory impairment ($p = 0.017$). [2]

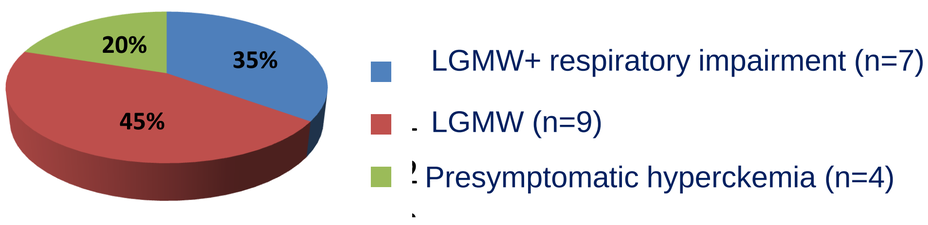
Aim of our study: To evaluate Central Nervous System involvement in a cohort of patients with LOPD using a multimodal approach.

PATIENTS

Patients with LOPD: 20 (F/M 12/8) - Mean age 50 (15) - Range 16-76

Inclusion Criteria: Age onset >1, Muscle residual GAA activity < 30 %, two pathogenic mutations identified on *GAA* genetic analysis

PATIENTS PHENOTYPES



Among these, 16 patients are on treatment with Enzyme Replacement Therapy (ERT)

METHODS

All patients were studied according to the following protocol:

- Brain study on 3T MRI scanner (Philips, Achieva)
  Morphological and angiographic evaluations were performed by 3D-FLAIR and 3D-TOF sequences, with a 32 channel coil.
  Fazekas scale was used to quantify white matter gliotic lesions whereas **Smoker's criteria** were applied to detect dolichoectasia at the basilar artery

  Functional MRI was performed to assess network functional connectivity: to verify the correlation between executive control network functional connectivity and clinical features of patients, considering functional connectivity maps of the salience (SN) and default-mode (DMN) networks (Rs-fMRI). All fMRI data were analyzed with FSL tool software.
- Neuropsycological battery tests: Montreal Cognitive Assessment (MOCA), Rey Auditory Verbal Learning Test (RAVLT), Wisconsin Card Sorting Test (WSCT).

Patients	Age	Disease duration (yrs)	Phenotype	Angio-CT results	CT results	CV risk factor	Brain MRI (Fazekas score)	Brain MRA (Smoker score)	MRA results
1	42	8	HyperCKemia	Normal	Temporo-insular lacunes	no	2	1	VBD
2	78	35	LGMW, RI	VBD	Nucleo-capsular lacunes	HBP	2	2	VBD
3	52	15	LGMW, RI	MCA M1 aneurysm (4mm) – VBD	Normal	no	2	2	MCA M1 aneurysm (4mm) – VBD
4	63	22	LGMW	VBD	Right ventricular trigone retraction due to ischemia	Smoke	2	3	VBD
5	70	32	LGMW +RI	VBD	Nucleo-capsular and subcortical WM lacunes	LDL	4	1	VBD
6	64	26	LGMW+RI+NIV	Basilar artery fenestration	Nucleo-capsular and temporo-insular lacunes	Smoke, HBP	4	1	Basilar artery fenestration
7	49	16	LGMW	VBD	Normal	no	2	2	VBD
8	50	3	LGMW+RI+NIV	Normal	Temporo-insular lacunes	no	1	1	VBD
9	18	8	LGMW	VBD	Normal	no	1	2	PCA
10	61	6	LGMW	VBD	subcortical WM lacunes	no	5	3	VBD
11	72	19	LGMW+RI+NIV	VBD	Temporo-insular lacunes	HBP,LDL	2	1	VBD
12	48	3	LGMW	Normal	Normal	no	1	1	VBD
13	18	9	HyperCKemia	np	np	no	1	0	n
14	56	31	LGMW+RI+NIV	Normal	Nucleo-capsular and subcortical WM lacunes	Smoke, LDL	4	2	VBD
15	15	8	HyperCKemia	np	np	no	1	1	VBD
16	21	14	HyperCKemia	Normal	Normal	no	1	0	n
17	41	5	LGMW	Normal	Normal	Smoke	1	1	VBD
18	63	20	LGMW	CA aneurysm (4,7 mm)	np	Smoke, LDL	4	4	CA aneurysm (4,7 mm)
19	50	30	LGMW	MCA M1 tract aneurysm (2mm)	Normal	Smoke	3	3	MCA M1 tract aneurysm (2mm)
20	54	6	LGMW	VBD	Normal	HBP, LDL	3	3	VBD

Tab. 1: LOPD Cohort characteristics. LGMW: Limb Girlde Muscle Weakness, RI: repsiratory impairment, NIV : non invasive ventilation, VA: Vertebral Artery, VBD: Vertebro Basilar Dolichoectasia, MCA: Middle Cerebral Artery, PCA: Posterior Cerebral Artery

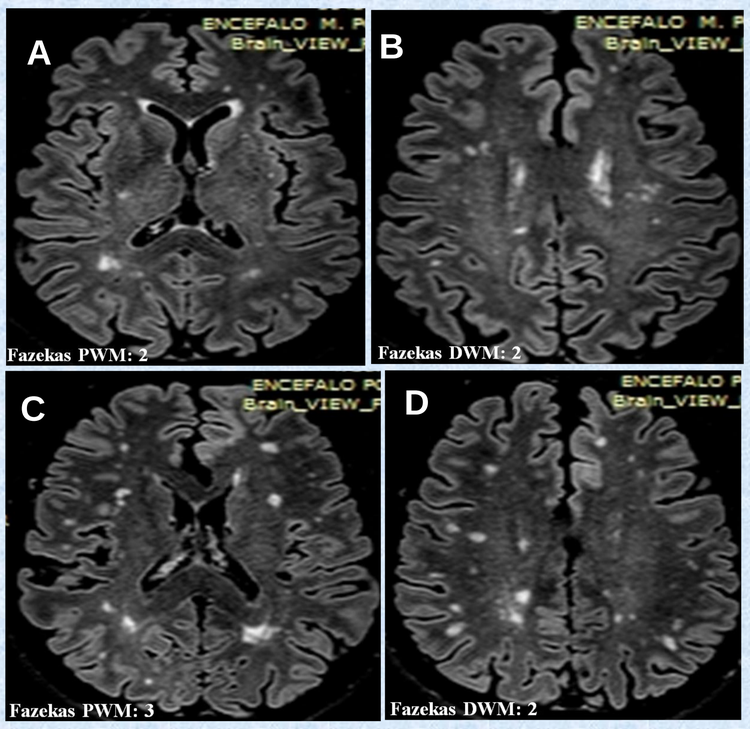


Figure 1: Brain MRI:T2-weighted seq: A, B: pt .18 (F/63), C, D: pt. 14 (F/56: presence of several gliotic lesions

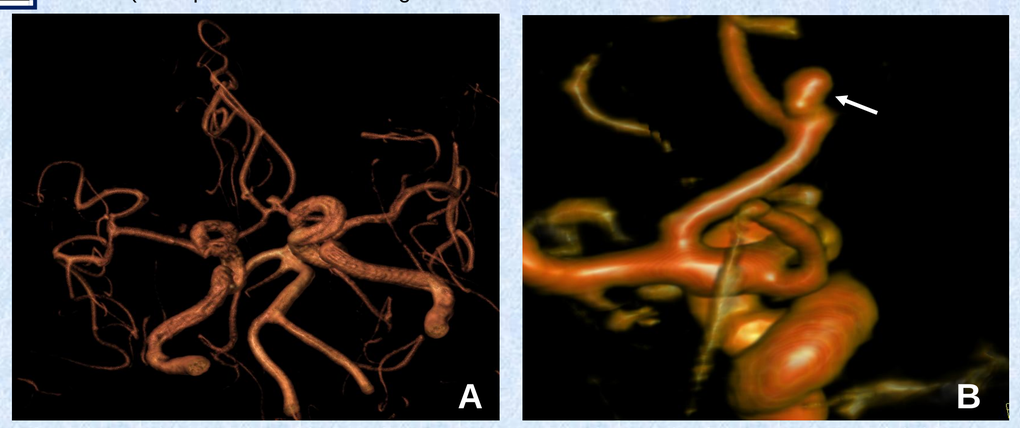


Figure 2 : Patient 18 : A. Evidence of VBD. B. Aneurysm of comunicating artery (4,7 mm) (white arrow)

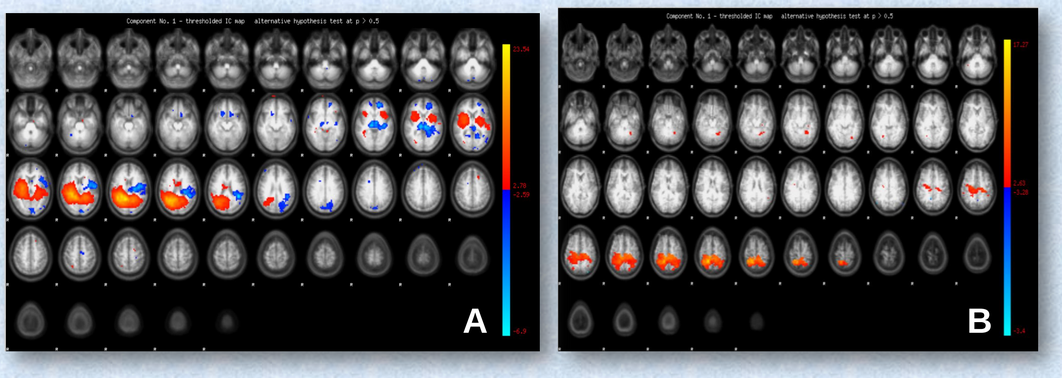


Figure 3 : Resting fMRI A. GROUP I (20-40 years); B. GROUP II (over 40 years): decreased connectivity in DMN networks, in both groups. In addition, the group II showed a decreased connectivity in the bilateral middle and superior frontal gyrus

RESULTS

Brain MRI and MRA

At MRI observations, Fazekas score was greatly abnormal in about 40% of patients (Figure 1)
According to Smoker's criteria, 10/20 patients had the dolichoectasia of vertebrobasilar system (Figure 2 A)

3/20 showed an unruptured intracranial aneurysm (UIA) involving the anterior circulation (MCA) (Figure 2 B)
One of them was immediately treated with endovascular coiling with great benefit.

Neuropsychological evaluation

- Using MOCA as a screening test (cut-off 26), 10/16 subjects showed a Mild Cognitive Impairment (10 subjects MOCA score 22 2; 16 subjects MOCA score 27 2). All patients with MCI have over 40 years.
- The memory areas were entirely preserved in all subjects.
- 10/20 subjects showed a Mild Cognitive Impairment. About 30% (6 pts) of subjects showed abnormal executive functions, as evidenced by Wisconsin assessment. All these patients were over 40 years.

Brain fMRI

Patients were divided in two groups: 20-40 (group I) and over 40 years (group II).

Significant cortical gray matter atrophy was found in group II, especially in frontal cortical areas, when compared with group I
Resting-state fMRI showed a decreased connectivity in DMN networks in both groups. In addition, the group II showed a decreased connectivity in the bilateral middle and superior frontal gyrus, indicating that these areas had a decreased component activity ($p<0.05$). (Figure 3)

CONCLUSIONS

In this group of patients with LOPD, MRI and MRA studies have revealed a recurrence of cerebrovascular brain alterations (aneurisms and VBDs) confirming that these aspects are underestimated manifestations of LOPD.

Neuropsycological evalutation evidenced a preservation of memory areas whereas an involvement of executive functions was found in 30% of pts

fMRI findings showed an abnormal functional connectivity and frontal gray matter atrophy in all patients, especially in the "over 40" group (group II) with a close correlation with neuropsychological assessment.

No correlations were found considering cerebrovascular risk factors and Fazekas score.

Our data suggests the opportunity to perform MRA or Angio-CT evaluation in Pompe patients in an attempt to detect earlier potentially treatable cerebrovascular malformations.

The pathogenesis of these rather new cerebrovascular aspects seems to be related to an hypoxic-ischemic mechanism, somehow linked to the enzyme deficiency.

REFERENCES

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