



Correspondence

Response: Late-onset Pompe disease manifests in the brain



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We acknowledge the comment to our recently published article that demonstrated no difference in the extent of white matter lesions (WML) in 19 late onset Pompe disease (LOPD) patients and 28 controls with similar cerebrovascular risk profile [1].

Finsterer [2] suggested that the finding of mild periventricular white matter lesions (PVWML) in one 49 year old LOPD patient (P18) with Fazekas score of 1 and no additional cerebrovascular risk factors should be commented on. It is well known that in general WML are a frequent MRI finding with prevalence between 45 and 95% in population-based studies. Mild PVWML like in patient P18 (with caps/lining) and punctuate deep/subcortical WML (DWML) occur in more than half of asymptomatic persons in age groups below 55 years [3]. However, the detailed etiology and pathogenesis of WML have not been understood so far. Many studies have demonstrated a clear correlation of WML with subject's age [4,5]. Likewise in LOPD patients this was demonstrated in our cohort and in others [6], [7]. It is therefore most likely that the mild PVWML observed in P18 present an ageing effect. This is supported by the fact, that also one of the two matched controls of this patient had PVWML with a Fazekas score 1.

The impact of various other risk factors of WML remains controversial [8]. However, we matched our LOPD with controls regarding the most frequently investigated vascular risk factors, including hypertension, obesity, hyperlipidemia, diabetes, and smoking. In our study it cannot be ruled out, that quality of risk factor treatment was different between LOPD and controls as this was not evaluated. This might have influence on the extent of WML. However, different quality of risk factor management would be a systematical error that effects results in patients and controls equally. It is further questionable, how information on risk factor treatment could be acquired realistically in the patients, since evolution of WML is a dynamic process that takes years. Optimally LOPD patients and controls would have to be continuously monitored over years in a prospective trial, which is hardly to realize.

Finsterer [2] suggested LOPD patients and controls without any concomitant diseases should than be compared. However, most LOPD patients in our cohort were elderly - nearly 85% with age \geq 45 years. Only one of those (and only 2 in total) had no concomitant risk factors.

In fact, hypertension was one of the most frequent risk factors in our cohort (LOPD 68%; controls 50%; $p = .83$). This prevalence lies within that of hypertension in the general population in our region (CARLA-study) with 74.3% for men and 70.2% for women in an age group between 45 and 83 years [9]. It seems therefore rather unlikely that relevant data on subjects at this age range without comorbidities (LOPD and controls) can be obtained.

On the contrary, we are increasingly dealing with elderly and multimorbid LOPD patients because of prolonged survival in the era of Enzyme replacement therapy (ERT). The interpretation of cerebral findings in these patients is therefore challenging and has to be set in the context of concomitant risk factors. The strength of our study is the comparison with two carefully matched controls for each patient to differentiate the impact of underlying LOPD from those associated with age and cerebrovascular risks.

We agree with Finsterer that LOPD has most likely an impact on cerebral pathology since glycogen storage occurs in cerebral vessels and brain tissue which is not reachable by the current ERT. In fact, our previous studies [10] and others confirm prominent vertebrobasilar ectasia in LOPD patients [6].

Regarding WML our results relativize the impact of the LOPD on their development in elderly patients. The similar extent of WML in LOPD patients and controls suggests a predominant effect of age and cerebrovascular risk factors for provoking the evolution of the cerebral changes.

However, correlation analysis of WML volume with risk factor number was significant in controls but not in LOPD (Table 1). Therefore there might be a marginal contribution of the disease itself to the development of WML. This might be interpreted as disease involvement.

Our results are in contrast to cerebral findings in CIOPD and might reflect the milder phenotype of LOPD due to residual enzyme activity. In summary our study contributes to better understanding of the evolution of WML in elderly LOPD with concomitant risk factors.

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Table 1
Correlation analysis of risk factor number with WML.

		r	Fazekas score (FS)			Volume WML
			DWML	PVWML	Total FS	
Risk factor number	LOPD (n = 19)	r	-0.26	-0.21	-0.30	-0.09
		p	0.36	0.06	0.49	0.69
	Controls (n = 38)	r	0.32	0.34	0.35	0.50
		p	0.046*	0.037*	0.03*	0.001*

Risk factors (for development of WML): diabetes mellitus, hypertension, hyperlipidemia, obesity, smoking; DWML deep white matter lesions; PVWML periventricular white matter lesions; WML white matter lesions; r Pearson correlation coefficient.

Bold values signifies $p < 0.05$.

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References

- [1] I. Schneider, O. Hensel, S. Zierz, White matter lesions in treated late onset Pompe disease are not different to matched controls, *Mol. Genet. Metab.* 127 (2) (2019) 128–131.
- [2] J. Finsterer, Late-onset Pompe disease manifests in the brain, *Mol. Genet. Metab. Rep.* 20 (2019) 100488.
- [3] R. Schmidt, H. Schmidt, J. Haybaeck, M. Loitfelder, S. Weis, M. Cavalieri, et al., Heterogeneity in age-related white matter changes, *Acta Neuropathol.* 122 (2) (2011) 171–185.
- [4] J. Lin, D. Wang, L. Lan, Y. Fan, Multiple factors involved in the pathogenesis of white matter lesions, *Biomed. Res. Int.* 2017 (2017) 9372050.
- [5] Group LS, 2001-2011: a decade of the LADIS (Leukoaraiosis and Disability) study: what have we learned about white matter changes and small-vessel disease? *Cerebrovasc. Dis.* 32 (6) (2011) 577–588.
- [6] F. Montagnese, F. Granata, O. Musumeci, C. Rodolico, S. Mondello, E. Barca, et al., Intracranial arterial abnormalities in patients with late onset Pompe disease (LOPD), *J. Inherit. Metab. Dis.* 39 (3) (2016) 391–398.
- [7] O. Musumeci, S. Marino, F. Granata, R. Morabito, L. Bonanno, T. Brizzi, et al., Central nervous system involvement in late-onset Pompe disease: clues from neuroimaging and neuropsychological analysis, *Eur. J. Neurol.* 26 (3) (2019) 442–e435.
- [8] B.M. Frey, M. Petersen, C. Mayer, M. Schulz, B. Cheng, G. Thomalla, Characterization of white matter hyperintensities in large-scale MRI-studies, *Front. Neurol.* 10 (2019) 238.
- [9] M.E. Lacruz, A. Kluttig, S. Hartwig, M. Loer, D. Tiller, K.H. Greiser, et al., Prevalence and incidence of hypertension in the general adult population: results of the CARLA-cohort study, *Medicine (Baltimore)* 94 (22) (2015) e952.
- [10] O. Hensel, I. Schneider, M. Wieprecht, T. Kraya, S. Zierz, Decreased outlet angle of the superior cerebellar artery as indicator for dolichoectasia in late onset Pompe disease, *Orphanet. J. Rare Dis.* 13 (1) (2018) 57.

Ilka Schneider*, Ole Hensel, Stephan Zierz
 Department of Neurology, Martin-Luther-University Halle/Saale, Ernst-Grube-Str. 40, 06120 Halle (Saale), Germany
 E-mail addresses: ilka.schneider@uk-halle.de (I. Schneider),
Ole.Hensel@medizin.uni-halle.de (O. Hensel),
Stephan.Zierz@uk-halle.de (S. Zierz).

* Corresponding author.