Characterization of 4L/PS-NA mice for cytokine activity and neurodegeneration

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BACKGROUND

Gaucher disease is the most common lysosomal storage disease. The neuronal disease variant is characterized by aggregated protein accumulations in the brain and associated neurological manifestations. It is autosomal recessively inherited and modeled by 4L/PS-NA mice that express low levels of prosaposin and saposins, as well as a functionally impaired β-glucosidase (GCase) with a homozygous point mutation at V394L. A detailed characterization of these mice already showed a strong inflammatory pathology in visceral and neuronal tissue (Schiffer et al., 2020). In this study inflammation processes and neurodegeneration in 4L/PS-NA mice were further analyzed.

MATERIAL and METHODS

We evaluated the plasma and CSF of 5, 12 and 18 weeks old 4L/PS-NA mice for KC/GRO (CXCL1), the mouse IL-8 homolog, using the MSD (Mesocale Discovery) immunosorbent assay. Neurofilament-light chain (NF-L) levels in plasma and CSF of 18 weeks old animals were analyzed using an ELISA from UmanDiognostics AB, Sweden.
To confirm neuronal loss, cerebellar cryo sections of 18 weeks old animals were immunohistologically labeled for calbindin, a Purkinje cell marker.

RESULTS

In the current study cytokines were assessed in the plasma and CSF of 4L/PS-NA mice and age-matched 4L/PS+/+NA littermates, representing animals with V394L GBA mutation, but endogenous saposin level.
While interferon-gamma or IL-1beta were not different between genotypes (data not shown), significant differences in KC/GRO concentrations between 4L/PS-NA and 4L/PS+/+NA littermates were detected in the plasma at 12 weeks of age (Fig. 1A).
In the CSF, this genotype-specific difference was more pronounced and additionally present at other assessed time points (Fig 1B).
Previously described neuronal loss, especially in the cerebellum of the 4L/PS-NA animals (Fig. 2C), was confirmed by highly increased NF-L levels in plasma and CSF of 18 weeks old animals, compared to 4L/PS+/+NA littermates (Fig. 2A,B).

SUMMARY and CONCLUSION

In summary, we can show that the previously presented strong neuroinflammation in several neuronal and visceral tissues is accompanied by high CXCL1 levels in the CSF and highly increased NF-L levels in the CSF and plasma. These data suggest that strong inflammatory processes are associated with neurodegeneration in Gaucher disease mouse model 4L/PS-NA.

RESULTS

Inflammation- KC/GRO

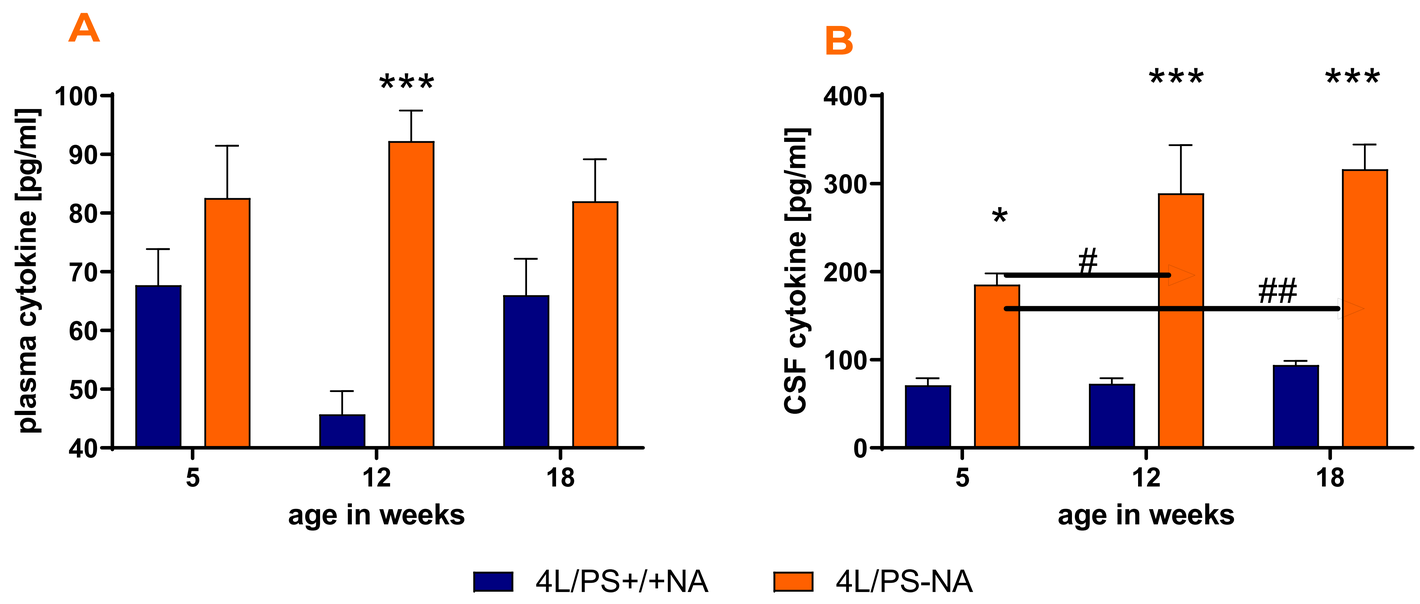

Figure 1. KC/GRO levels in the plasma and CSF of 4L/PS-NA mice over age.
A: KC/GRO levels in pg/mL in the plasma and **B:** CSF of 4L/PS-NA mice compared to 4L/PS+/+NA at the age of 5, 12 and 18 weeks. Two-way ANOVA followed by Dunnet's multiple comparison test. *genotype differenced; #age differences. Mean + SEM. */#p<0.05; ##p<0.01;***p<0.001.

NF-L and Neuronal Loss

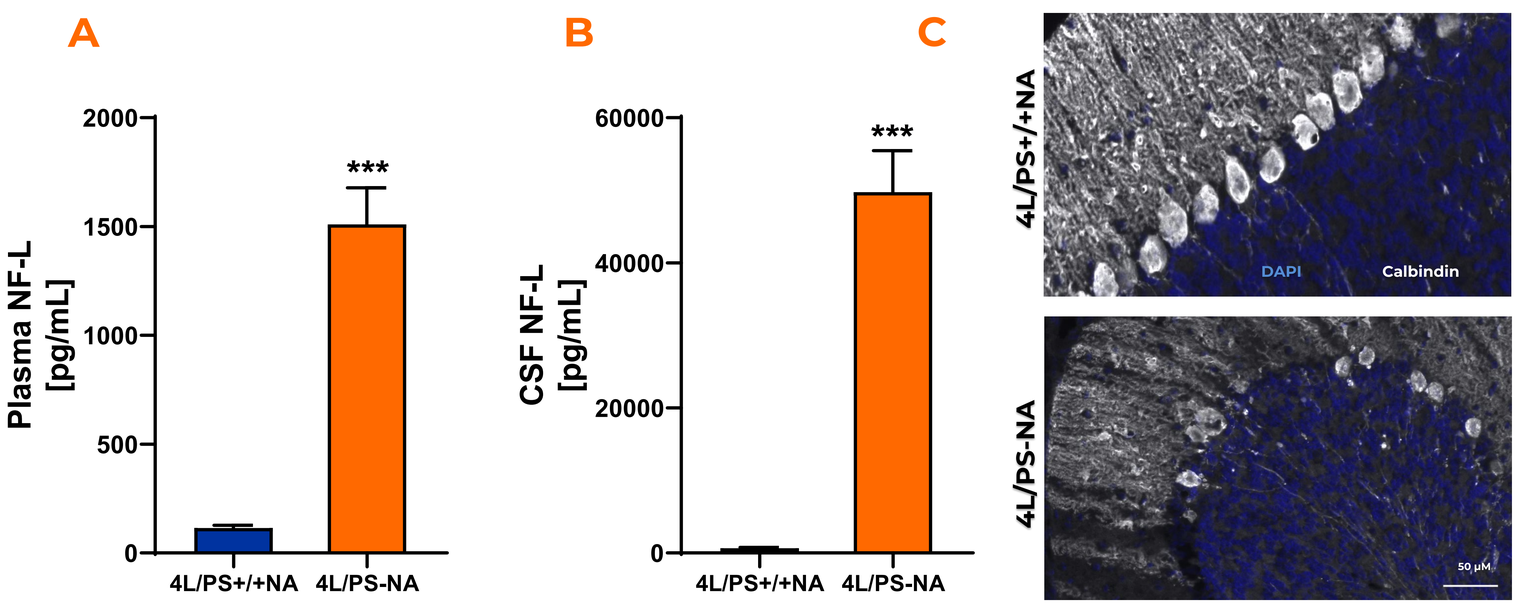

Figure 2. Neuronal loss in 18 weeks old 4L/PS-NA mice.
A: Neurofilament-light chain levels in pg/mL in the plasma and **B:** CSF of 4L/PS-NA mice compared to 4L/PS+/+NA. Unpaired t-test. Mean + SEM. ***p<0.001. **C:** Representative images of Calbindin (white) and DAPI (blue) immunolabeling in 4L/PS-NA and 4L/PS+/+NA mice.

REFERENCES

Schiffer et al., 2020. Characterization of the visceral and neuronal phenotype of 4L/PS-NA mice modeling Gaucher disease. PLoS One. Jan 13;15(1):e0227077. PMID: 31929594.
Loeffler T, Schilcher I, Flunkert S, Hutter-Paier B. Neurofilament-Light Chain as Biomarker of Neurodegenerative and Rare Diseases With High Translational Value. Front Neurosci. 2020 Jun 11;14:579. PMID: 32595447.

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