Neuropathological correlates of ocular motor deficits in progressive supranuclear palsy (PSP)

Sigrun Roeber¹, Vera Ogunlade¹, Hans Kretzschmar¹, Anja Horn²
1 IFBlMU and Institute of Neuropathology, Ludwig-Maximilians-University
2 IFBlMU and Institute of Anatomy, Department I, Ludwig-Maximilians-University

Introduction

Progressive supranuclear palsy (PSP) is a tauopathy clinically characterized by eye movement disorders, e.g. slowing and loss of vertical saccades, later slowing and loss of horizontal saccades with intact VOR, ending up in a complete gaze palsy. Further symptoms include postural instability and early falls. With histochemical markers (e.g. non-phosphorylated neurofilaments, parvalbumin) the premotor brainstem cell groups of the saccadic and VOR system have been identified in human and now they are assessed in PSP cases from the brain bank to study degenerative changes. Here, specifically the questions are addressed:

- Is there a correlation between eye movement deficits and degeneration in premotor and/or motor neurons of the oculomotor system in PSP patients?
- Which methods can be used for quantification of degenerative changes?

Methods

The clinical history of 45 archival and 4 new PSP cases from the brain bank the clinical reports were screened for history of oculomotor deficits. From 36 archival and 2 new cases with clinical reports the available tissue of so far 24 and 2 cases was screened for relevant brainstem regions, which in some cases had to be recovered from formalin and were embedded in paraffin for histological processing. Adjacent paraffin sections of oculomotor brain-stem regions were immunostained for histochemical markers identifying the relevant cell groups (parvalbumin, non-phosphorylated neurofilament) and abnormally phosphorylated tau protein (AT8) revealing degeneration. While still screening the remaining 14 cases a semi-automatic quantitative analysis of AT8-positive profiles was performed on 2 PSP cases with a trial version of HistoQuant-Software (3D Histotech) on scanned slides (Zeiss, MiraxMid). AT8-positive neurons and glial cells were manually counted in defined areas.

Results

Both PSP cases show deposits of hyperphosphorylated tau protein (AT8-staining) in premotor areas for vertical and horizontal eye movements, but at different degree in different cellular compartments. Glial AT8-positive deposits and threads are present in premotor regions for horizontal (PPRF) and vertical (RIMLF) eye movements in both cases, but to a higher degree in the “late” PSP case 2 (Fig. 3 and 6), where strong additional neuronal staining of premotor and even moto-neurons is prominent. Although the semi-automatic quantitative method largely resembles the results of visual inspection of AT8-staining (Fig. 6A), the manual counting of affected glia and neurons is required to reflect the functional deficit.

Conclusion

- Functional oculomotor cell groups can be identified in archival tissue and now be targeted for a further investigation of the tau-load.
- Tau-deposition in glia and neuronal processes precedes the affection of neuronal cytoplasm
- Tau-deposition in premotor areas precedes the involvement of motoneurone
- The extent of tau-pathology corresponds to the severity of oculomotor deficits.
- The results support the hypothesis that the disease PSP may progress along neuronal pathways in an anterograde fashion.
- The parameters for quantification are critical for the interpretation of the results and have to be worked out carefully.