Is posterior cortical atrophy an extreme phenotype of GRN mutations?

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INTRODUCTION

Posterior cortical atrophy (PCA)1 is a rare neurodegenerative disorder affecting primary visual occipital, occipito-temporal and bi-parietal cortices. PCA is usually considered as atypical variant of Alzheimer’s disease (AD) because most cases had AD pathology 2,3. The genetic basis of PCA remains elusive. Mutations in PSEN1, PRNP and IT15 genes have been identified in few patients 4,5,6. A link between PCA and genetic forms of FTLD is supported by the recent recognition of a MAPT mutation in one PCA case 7.

We identified a GRN mutation in a patient presenting with visual deficits, apperceptive visual agnosia and occipital cortical atrophy, fitting the criteria of PCA.

DISCUSSION

A p.Arg110* GRN mutation was identified in a patient with a clinical phenotype of PCA characterized by prominent visual deficits, apperceptive visual agnosia, alexia, prosopagnosia with preservation of other cognitive functions. He presented predominant atrophy of the primary visual cortex, and of the parieto-occipital region that was in agreement with the criteria of visual/ventral variant of PCA 1,2. The clinical presentation of patient 004 was very unusual because isolated visual agnosia at onset has never been reported in GRN carriers, mostly presenting bvFTLD, PNFA or CBS. The distribution of atrophy was also different from GRN carriers, where usually involves frontal, temporal and parietal cortex but preserves occipital regions at onset 8.

GRN mutations are characterized by TDP-43 pathology and no pathological cases of PCA with TDP-43 inclusions have been described so far. In our patient, AD pathology cannot be ruled out, in absence of brain pathology and CSF analyses. However, the patient did not carry the strong ApoE ε4 risk allele for AD and the atrophy rapidly progressed to severe dorsal cortical involvement.

CONCLUSION

This study extends the clinical spectrum of GRN mutations and demonstrates that, in rare cases, the pathology can be confined to posterior cortex at onset. GRN analyses could be included in PCA, particularly when the damages progress to anterior cerebral regions and a family history of dementia is present. FTLD genes analyses patient’s cohorts will be necessary to better evaluate their genetic contribution to PCA. Finally, this study underlines a possible continuum in degenerative dementias, and highlights the limits of actual nosological boundaries. Clarifying these boundaries by identifying factors driving phenotypic heterogeneity will have important implications for the definition of new diagnosis criteria of degenerative dementias and clinical trial recruitment in the future.

REFERENCES