Clinical and neuroimaging findings in a cluster of progranulin C157KfsX97 mutation

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Background and Objectives

Frontotemporal lobar degeneration (FTLD) is a group of neurodegenerative diseases displaying high clinical, pathological and genetic heterogeneity. Among the most recurrent causes of familial FTLD there are progranulin gene (*GRN*) mutations. In the present study we describe the clinical and neuroimaging phenotypes in a cluster of five apparently unrelated patients displaying the progranulin C157KfsX97 mutation.

Patients and Methods

Our cluster comprises five male patients affected by a syndrome within FTLD spectrum. Following the finding of low values of plasma progranulin dosage, the presence of progranulin C157KfsX97 mutation was demonstrated in all cases. Only four patients presented a positive familial history, even if the results of haplotype sharing analysis suggested a common ancestry for all of them. Two clinical phenotypes were identified: behavioural variant of frontotemporal dementia (bvFTD; 3 patients, 2 with prevailing apathetic and 1 with prevailing dysexecutive symptoms) and corticobasal syndrome (CBS; 2 patients). MRI was performed in all, PET-FDG studies in four and SPECT-perfusion study in one. Functional neuroimaging studies were visually evaluated. In addition a semi-quantitative voxel based analysis was performed at individual level in 3 patients (one with CBS phenotype and 2 with bvFTD) using SPM2. In each out of these 3 patients FDG uptake was compared to that of a group of 16 controls (age range of controls: 39-72) using the single subject condition covariate model.

Results

Disease duration was (mean/SD) 3±2.9 years, age 63±5 years, MMSE 21.8±4.2, FAB 7.2±4.76. MRI revealed cortical atrophy in all, diffuse in 2, mild and located in the fronto-parietal regions in one, severe cortico-subcortical in 2. Atrophy was asymmetric in 4 patients. In bvFTD cases, glucose hypometabolism/ hypoperfusion was asymmetric and more marked in the frontal lobe (including prefrontal dorsolateral and medial regions), anterior cingulate cortex, inferior (BA40) and superior (BA7) parietal cortex, posterior cingulate/medial precuneus and to a lesser extent temporo-parietal and temporal regions. In the CBS variant, a similar involvement of frontal and parietal cortex was found together with ipsilateral thalamic and striatal hypometabolism, whereas the posterior cingulate appeared less involved.

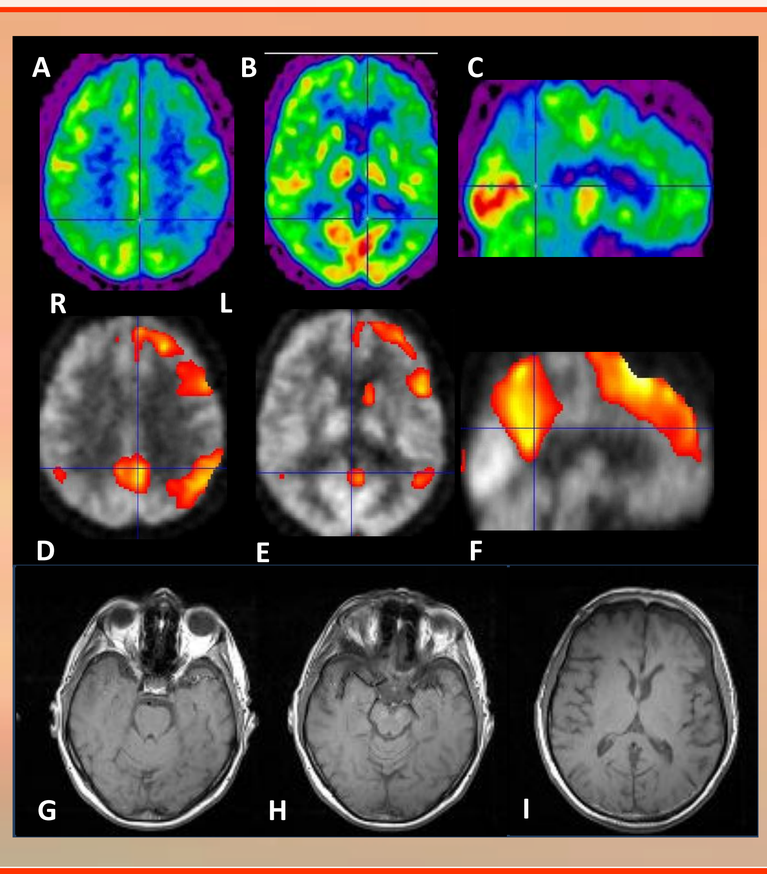

Figure 1.
Axial (A,B) and sagittal (C) PET scans in a patient affected by bvFTD show glucose hypometabolism (45-60 mins after ^{18}FDG injection) in frontal, parietal, temporo-parietal and posterior cingulate cortex (PCC) prevailing on the left. SPM analysis, matched with 16 control subjects, (D, E, F) makes those alterations, in particular in PCC, more evident. T1-weighted MRI images (G, H, I) evidence frontal and anterior temporal atrophy with hippocampal sparing. This patient presented deficits in verbal and spatial memory, behavioural and executive functions, likely due to the pattern of metabolic alterations.

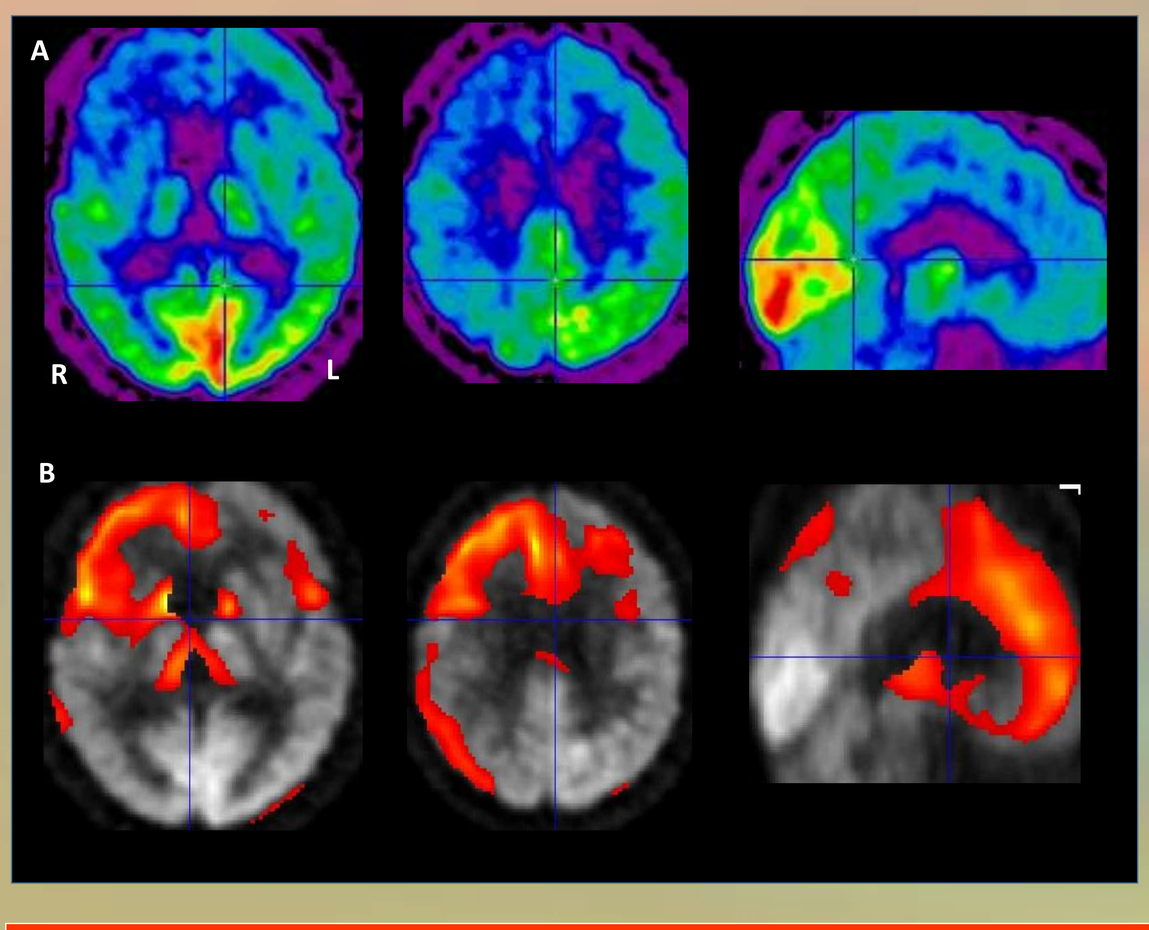

Figure 2.
A: In a CBS patient PET-FDG images show reduction of relative glucose metabolism in the frontal lobe and anterior cingulate cortex bilaterally but more marked on the right side. Relative glucose metabolism was also reduced to a lesser extent the right parietal cortex, striatum and thalamus bilaterally mostly on the right side.
B: SPM single subject analysis vs a group of controls highlights the regional patterns of reduced glucose metabolism.

Discussion and conclusions

The reported data indicate that in our cluster, which is the first one described with apparently unrelated *GRN* C157KfsX97 mutations, significant heterogeneity exists both in clinical presentations and in neuroimaging features. The patterns of hypometabolism/ hypoperfusion were associated with the cognitive/clinical phenotypes. Overall, frontal and parietal involvement are a distinctive aspect of GRN-mutated FTLD, irrespectively of the specific mutation; that could be easily explained by the common pathogenic mechanism, i.e. haploinsufficiency.

References

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