Patients with progranulin mutations overlap with the progressive dysexecutive syndrome: towards the definition of a frontoparietal dementia phenotype

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We read with great interest the article by Townley et al. (2020), which described a series of 55 patients with progressive early-onset dementia with a predominant impairment in the executive functions with probable Alzheimer’s disease. They thoroughly characterize these patients, who show a consistent impairment of executive functions rather than behavioural changes, defining the progressive dysexecutive syndrome. These patients consistently revealed hypometabolism in parietofrontal brain regions. All the patients had positive amyloid biomarkers and the great majority (48/55) also had positive tau biomarkers. Two of the patients had pathological confirmation of the diagnosis. Yet, genetic test was only performed in eight patients and only looking for the autosomal dominant mutations associated with Alzheimer’s disease. In fact, the authors carefully state that this presentation may not be specific to Alzheimer’s disease, but report only those cases, as Alzheimer’s disease is probably the most common cause of this syndrome. This is a very interesting paper, defining a new subset of patients with cognitive impairment. Deep phenotyping is a potent tool for personalized medicine and for the understanding of new syndromic entities.

In this letter, we describe our cohort of patients with GRN (progranulin) mutation, including Cerebrospinal Fluid (CSF) findings, and discuss the similarities with those of the proposed progressive dysexecutive syndrome. The serum GRN level assessments and the mutation analysis in this gene were performed as previously described by our group (Almeida et al., 2014). CSF samples were collected as part of the routine clinical diagnostic protocol. Pre-analytical and analytical procedures were done in accordance with the Alzheimer’s Association guidelines for CSF biomarker determination (Mattsson et al., 2011). CSF samples were collected in sterile polypropylene tubes, immediately centrifuged at 1800 × g for 10 min at 4°C, aliquoted into polypropylene tubes and stored at −80°C until analysis. CSF Aβ42, total-Tau and
phosphorylated-Tau (p-Tau) were measured separately by commercially available sandwich ELISA kits (Innotest, Fujirebio, Belgium), as previously described (Kapaki et al., 2001; Baldeiras et al., 2009). External quality control of the assays was performed under the scope of the Alzheimer’s Association Quality Control Program for CSF Biomarkers (Mattsson et al., 2011). Neuropsychological studies’ methodology and results are reported elsewhere (Lima et al., 2020). The study was approved by the ethics committee of our hospital, and biological samples were obtained following written informed consent from the legal representatives.

Interestingly, it has been previously demonstrated that GRN mutation carriers may show a phenotype resembling Alzheimer’s disease, with marked memory impairment associated with frontal lobe changes (Le Ber et al., 2008; Kelley et al., 2009; Hallam et al., 2014). Peculiar features like early visuospatial and working memory deficits (Hallam et al., 2014) and parietal signs such as apraxia and dyscalculia have also been described (Rohrer et al., 2008), which correlate with early temporal, parietal and insular atrophy (Whitwell et al., 2007; Rohrer et al., 2015). There are additional similarities between GRN patients and the group reported in the paper by Townley et al. (2020). Of notice, two patients had parkinsonism, with one of them having a previous diagnosis of corticobasal syndrome. Twenty-four out of 31 patients had language involvement, and 28 out of 40 had ideomotor apraxia. All of these findings are common on GRN mutation carriers (Le Ber et al., 2008; Hallam et al., 2014). In our cohort, GRN mutation carriers have worse scores in executive functions, initiative and psychological control than both Alzheimer’s disease and behaviour-variant frontotemporal dementia (bvFTD) patients matched for age, severity and education (Lima et al., 2020). Regarding memory, GRN patients presented with a transitional performance between sporadic bvFTD and Alzheimer’s disease. They are better than Alzheimer’s disease on measures of both immediate and delayed recall but worse than sporadic bvFTD. Focusing on parietal functions, these patients also exhibit a visuospatial pattern of performance that includes features of both sporadic bvFTD and Alzheimer’s disease patients, with lack of elements and gestalt changes (features from Alzheimer’s disease) and also with perseveration and lack of planning (sporadic bvFTD features). Consistent with the progressive dysexecutive syndrome patients, GRN mutation carriers have been shown to have more complaints on executive functions and less complaints on social changes than other ubiquitin-positive Frontotemporal dementia (FTD) (Van Deerlin et al., 2007). In fact, this different profile of GRN mutation carriers has been previously reported (Beck et al., 2008), with these patients characteristically less frequently showing disinhibition, loss of empathy, aggression and obsessive behaviour.

Regarding Alzheimer’s disease biomarkers, of our cohort of GRN mutation carriers, 21 patients have had collected CSF Alzheimer’s disease biomarkers. Of these, six (28.6%) had abnormal CSF amyloid-β42, with an additional four (adding up to 47.6%) having very borderline values. In terms of CSF total-Tau, 16 (76.2%) had increased values. Concerning p-Tau, eight (38.1%) had increased values. Considering the A/T/N classification scheme (Jack et al., 2016), eight (38.1%) patients are A−/T+/N+ and another three (14.3%) are A+/T−/N+. Together with the neuropsychological data, this might have led to a diagnosis of Alzheimer’s disease or Alzheimer’s disease variants in half of the patients by some criteria (Dubois et al., 2014). However, no patients were A+/T+/N+ or A+/T+/N− (two A+/T−/N+ had borderline p-Tau and one A−/T+/N+ had borderline CSF amyloid-β42).

The neuropsychological and imaging data place GRN mutation carriers in an intermediate position between Alzheimer’s disease and FTD. For a number of reasons, they stand out of the standard FTD phenotype: they frequently have parietal and memory impairment; they show insular and parietal atrophy; they may present as corticobasal syndrome; and they are very rarely associated with amyotrophic lateral sclerosis (Guerreiro et al., 2020). The mixed CSF biomarkers profile further complicate the distinction.

This report has some limitations; the A/T/N comprises other biomarkers that we did not include in this report and could give additional information. The use of both total-Tau and p-Tau may have some limitations, given their correlation. However, this report gives data on real-world evidence with a substantial amount of patients, whose results may guide both further research studies and the clinical approach.

In conclusion, GRN-associated FTD has a great overlap with the progressive dysexecutive syndrome patients. Hence, this new subset of patients defined by Townley et al. (2020) may be very much justified, as it may harbour not only a specific anatomical pattern of parieto-frontal dysfunction but also a specific genetic background, such as GRN, and possibly others, such as the recently reported CYLD (Dobson-Stone et al., 2020; Tábuas-Pereira et al., 2020). GRN mutations should always be suspected in this setting, regardless of CSF biomarkers, especially if new gene-targeting treatments arise.

**Data availability**

Data are shown within the paper. Additional information is available upon request to the corresponding author.

**Competing interests**

The authors have no competing interests to declare.
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