Hereditary dystonia and parkinsonism: two sides of the same coin?

This scientific commentary refers to ‘Parkinson’s disease in GTP cyclohydrolase 1 mutation carriers’, by Mencacci et al. (doi:10/1093/brain/awu179).

A number of inherited disorders are marked by combined dystonia and parkinsonism, and the genetic basis of many of these has now been identified. They include putative ‘neurofunctional’ conditions with dystonia-parkinsonism, such as DOPA-responsive dystonia caused by mutations in the GTP cyclohydrolase 1 (GCH1) gene, as well as neurodegenerative diseases that present with predominant parkinsonism, frequently accompanied by dystonic features, i.e. ‘parkinsonism-dystonia’, as seen in carriers of parkin (PARK2) and PINK1 mutations. Because dystonia can be the presenting sign in parkinsonism-dystonias (Grünewald et al., 2013) and, conversely, patients with DOPA-responsive dystonia can present with isolated parkinsonism (Grimes et al., 2002; Tadic et al., 2012), it can be difficult to categorize individual patients solely on clinical grounds. The boundaries between dystonia and parkinsonism may thus be less well defined than previously thought, and this calls for detailed longitudinal phenotyping of patients. Indeed, despite the advent of next-generation sequencing and increased availability of diagnostic testing—resulting in a wealth of genetic data—systematic genotype-phenotype evaluations lag behind advances in genetics and have largely yet to be translated into clinical practice (Grünewald et al., 2013).

In this issue of Brain, Mencacci et al. elegantly address the phenomenon of prominent parkinsonism in carriers of GCH1 mutations (Mencacci et al., 2014). Prompted by their observation that relatives of patients with DOPA-responsive dystonia can present with pure ‘Parkinson’s disease’, they systematically collected and examined four such unrelated pedigrees harbouring GCH1 mutations and reviewed the literature for similar reports. This resulted in a total of eight cases from different ethnic backgrounds with predominant parkinsonism, all of whom had a mostly asymmetrical reduction in dopamine transporter density or fluorodopa uptake, in keeping with degeneration of dopaminergic neurons (Mencacci et al., 2014). Based on this finding, the authors hypothesized that sporadic Parkinson’s disease can also be caused by mutations in GCH1. To test this idea, they evaluated in-house whole exome data from 1318 patients with Parkinson’s disease and 1635 controls, as well as 4300 additional control data sets from the Exome Variant Server (EVS), for mutations in GCH1. This revealed 11 heterozygous non-synonymous variants of GCH1, 10 of which were detected in patients with Parkinson’s disease, three only in controls, and two in both groups. The reported frequency of putative GCH1 mutations (0.75%) was significantly higher in patients with Parkinson’s disease than in controls (0.1%) (Mencacci et al., 2014). Using a more conservative approach to this calculation, i.e. only including those GCH1 variants that are exclusively present in patients with Parkinson’s disease and likely to be disease-causing based on the four in silico prediction programs used by the authors, results in a mutation frequency of only 0.38% among patients. However, when compared to the frequency in the combined controls (in-house and EVS), this difference remains significant (P=0.001; Fisher’s Exact Test). Indeed, there is no doubt that parkinsonism is an important feature of DOPA-responsive dystonia, and it can even be the only manifestation of a GCH1 mutation (Grimes et al., 2002; Tadic et al., 2012). Nevertheless, due to the reduced penetrance and highly variable expressivity of GCH1 mutations, as well as their overall rarity among both patients and controls—they are present at frequencies well below those of the single nucleotide polymorphisms used in association studies—the question when trying to disentangle the relationship between GCH1 mutations and parkinsonism is more one of causation than association.

Supporting this view, Tadic et al. (2012) reviewed the DOPA-responsive dystonia literature in a recent comprehensive meta-analysis and revealed some interesting clinical-epidemiological details with respect to parkinsonism: first, parkinsonism is indeed relatively common in GCH1 mutation carriers (27% have parkinsonism and 82% dystonia); and second, the frequency of parkinsonism is dependent on the age of onset of dystonia (26% in
GCH1 mutation carriers with onset below the age of 15 years, and 53% in those with disease onset after age 15 years (Tadic et al., 2012).

In our own cohort of 15 GCH1 mutation carriers, nine had obvious clinical signs of parkinsonism, including two patients with overt, classical parkinsonism leading to a diagnosis of idiopathic Parkinson’s disease. Notably, however, one of our two patients with ‘Parkinson’s disease’ carrying the known c.206C>T; p.P69L GCH1 mutation (Furukawa et al., 2004) had first presented with foot dystonia at the age of 6 years. Dystonic symptoms showed only mild progression and diurnal fluctuations were never observed. In her 20s the patient developed a resting and action tremor of her left hand that subsequently generalized. After a pregnancy at the age of 30 years, a generalized bradykinesia was noted and the patient started on levodopa therapy. The initial excellent treatment response lasted for only a few months, requiring an increase in dose and, several years later, resulting in generalized levodopa-induced dyskinesias. Now, at the age of 63 years, the patient shows additional marked walking difficulties due to bradykinesia, freezing, and postural instability. Indeed, our case report closely resembles those described by Mencacci et al. (2014). Several of their patients also showed early-onset dystonia initially, followed by the development of parkinsonian features that later dominated the phenotype and thus led to a diagnosis of Parkinson’s disease.

As well as giving rise to a broad spectrum of motor symptoms and a variable disease course, GCH1 mutations can also remain entirely non-manifest, a phenomenon referred to as reduced penetrance. Although reduced penetrance is well recognized, especially in males, it is unpredictable in individual cases of DOPA-responsive dystonia. This poses a challenge for counselling the families of mutation carriers, and complicates the evaluation of the potential pathogenicity of (new) GCH1 variants. This latter issue is illustrated by one of our asymptomatic cases carrying the c.610G<A; p.V204I variant of GCH1: a variant described by Mencacci et al. as the likely recurrent pathogenic variant in 3 of 10 patients with Parkinson’s disease in their exome sequencing study. As this variant was additionally seen in one EVS control, an alternative possibility is that it represents a rare benign variant. Intriguingly, one of the probands studied by Mencacci et al. (2014) harbours the pV204I change in the compound-heterozygous state. This patient, however, presented with a classical form of DOPA-responsive dystonia rather than with the much more severe, infant-onset phenotype that typically characterizes compound-heterozygous GCH1 mutation carriers (Brüggemann et al., 2012), further calling into question the pathogenicity of this particular variant.

Other monogenic dystonias may also be accompanied by signs of parkinsonism, adding a further layer of complexity to the relationship between dystonia and parkinsonism. For example, a patient with DYT1 dystonia was originally misdiagnosed with Parkinson’s disease due to a prominent (dystonic) tremor (Klepińska et al., 2013). Likewise, patients with myoclonus-dystonia due to mutations in the epsilon-sarcoglycan gene may exhibit parkinsonian features and may even have a good response to high-dose levodopa treatment (Luciano et al., 2009). These examples further highlight the importance of genetic testing in establishing the definitive causes of movement disorders.

A final key question in the Mencacci et al. article is whether neurodegeneration may be a consequence of GCH1 mutations. In line with this idea, all four of their patients had a documented presynaptic dopaminergic deficit, as did the four cases they identified in the literature. In further support of this notion, several of our own patients presented with mirror movements and developed dyskinesias or even dementia, i.e. features usually seen in the context of neurodegeneration. Interestingly, parkinsonian signs were also reported as a relatively common residual motor sign in GCH1 mutation carriers following treatment, with an age-of-onset-dependent frequency ranging from 17–24% (Tadic et al., 2012).

Mencacci et al. propose the intriguing hypothesis that some GCH1 mutation carriers may be able to compensate for the effect of the mutation, i.e. haploinsufficiency of GCH1, for decades but later go on to develop neurodegeneration. A better understanding of the underlying brain network changes, and of potential compensatory mechanisms and the failure thereof, will be important for predicting disease manifestation and expression in individual mutation carriers. In this context, results from prospective clinical, detailed neuroimaging, and electrophysiological studies of GCH1 mutation carriers with different phenotypic presentations—including non-manifesting, dystonia, and predominant parkinsonism—may serve as potential endophenotypes.

Most importantly, the question arises as to whether these findings and considerations might have clinical implications even today: could neurodegeneration be avoided by (lifelong) dopaminergic replacement therapy? There is at least anecdotal evidence that early treatment can decrease or even prevent developmental delay in children with compound-heterozygous GCH1 mutations (Brüggemann et al., 2012), suggesting that low-dose levodopa treatment could possibly be considered as a preventive measure, also in heterozygous non-manifesting GCH1 mutation carriers.

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References


Neuronal substrate of cognitive impairment in post-stroke dementia

This scientific commentary refers to ‘Pyramidal neurons of the prefrontal cortex in post-stroke, vascular and other ageing-related dementias’, by V. Foster et al. (doi: 10.1093/brain/awu172).

Post-stroke dementia is a frequent cause of loss of independence following stroke, whereas post-stroke cognitive decline affects an even greater number of stroke survivors. The burden of post-stroke dementia and cognitive decline is likely to increase because of falling mortality rates after stroke, the ageing of Western populations, and longer life expectancies in developing countries. However, the pathological processes that increase vulnerability to cognitive decline in previously non-demented stroke survivors are unknown. In this issue of Brain, Foster et al. provide new clinico-pathological evidence that selective regional pyramidal neuron atrophy in the dorsolateral prefrontal cortex, rather than a change in neuronal density per se, is associated with executive dysfunction in post-stroke dementia and vascular dementia (Foster et al., 2014).

The neuropathology of vascular cognitive impairment remains controversial for several reasons. First, cerebrovascular lesions are heterogeneous in nature (vessel wall modifications, perivascular tissue alteration, myelin loss in white matter, infarcts or haemorrhages, etc.), in size (from microscopic cortical infarcts to large territorial infarcts), and in location, being widely distributed throughout the brain (cortex, deep or periventricular white matter, basal ganglia, hippocampus). Each cerebrovascular lesion may have an impact on cognition through various mechanisms including altered blood flow and oxygen supply, chronic inflammation, disruption of axonal tracts, or altered cortical connectivity (Iadecola, 2013). Second, the link between chronic cerebrovascular lesions and cognition is still disputed, especially given frequent reports of neuroimaging abnormalities attributed to vascular mechanisms in the brains of cognitively normal subjects. Finally, the exploration of clinico-pathological correlations in vascular cognitive impairment suffers from the absence of a reliable, harmonized and widely accepted protocol for quantification of the cerebrovascular burden in post-mortem brains, despite recent attempts to create one (Deramecourt et al., 2012).

Although dysexecutive syndrome has long been regarded as the predominant feature of vascular cognitive impairment, and has been linked to the disruption of frontal-subcortical neuronal circuits, the precise mechanisms and pathological changes underlying dysexecutive syndrome remain unclear. White matter changes, globally and regionally assessed with quite simple imaging rating scales, were associated with executive dysfunction and reductions in processing speed in several subtypes of mild cognitive impairment (Debette et al., 2007). However, such rating scales may lack validity for explaining cognitive performance. More detailed analyses of grey and white matter, using voxel-based morphometry and diffusion tensor imaging, are needed. Coupled with cognitive assessment, these approaches have produced convergent results, revealing widespread structural alterations in the frontal and parietal lobes of patients with early brain microangiopathy (Quincke et al., 2012). Changes in processing speed, one of the main components of executive function, have been related to disruption of frontal-subcortical circuits, particularly in dorsolateral prefrontal and anterior cingulate areas, in patients with the small vessel disease, CADASIL (Duering et al., 2012). These subcortical alterations were recently found to correlate with a significant frontal cortical thinning and atrophy in the thalamus, putamen and globus pallidus, suggesting degeneration of neurons in these regions (Thong et al., 2014).

Foster et al. now reveal pathological changes related to executive dysfunction in three main clinical variants of vascular cognitive impairment: post-stroke dementia, subcortical ischaemic dementia and mixed Alzheimer’s disease and vascular dementia. Their work extends the pathological spectrum of cerebrovascular lesions, to include neuronal atrophy (Foster et al., 2014). Using thorough stereological methods and robust cell morphometric analysis, they show reduced cell volume (but not reduced density) of pyramidal neurons in layers III and V of the dorsolateral prefrontal cortex in patients with vascular cognitive impairment, compared to post-stroke non-demented patients and controls. Notably, the changes in cell volume correlated with the degree of post-stroke cognitive impairment. Their observations suggest a vascular base...