

## LETTER TO THE EDITOR

### Parkinsonism in GTP cyclohydrolase 1-deficient DOPA-responsive dystonia

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Sir,

We read with great interest the article entitled ‘Parkinson’s disease in GTP cyclohydrolase 1 mutation carriers’ published recently by Mencacci *et al.* (2014); the enzyme GTP cyclohydrolase 1, encoded by the *GCH1* gene, catalyzes the rate-limiting step in the biosynthesis of tetrahydrobiopterin (the essential cofactor for tyrosine hydroxylase). Using <sup>123</sup>I-N-*ω*-fluoropropyl-2-β-carbomethoxy-3-β-(4-iodophenyl) tropane, the authors found abnormal imaging of dopamine transporter (DAT) single photon emission computed tomography (SPECT) in four adult-onset parkinsonian patients associated with *GCH1* variants from four unrelated pedigrees with autosomal dominant GTP cyclohydrolase 1-deficient DOPA-responsive dystonia [DYT5a; the major form of DOPA-responsive dystonia (Furukawa *et al.*, 2013)]. In addition, analysing whole-exome sequencing data of 1318 parkinsonian and 5935 control cases, the authors identified 11 different heterozygous *GCH1* variants and have stated that rare *GCH1* mutations are associated with an increased risk of Parkinson’s disease. Consequently, they have suggested that normal striatal <sup>18</sup>F-fluorodopa uptake reported previously in patients with *GCH1*-parkinsonian phenotype (Nygaard *et al.*, 1992; Furukawa *et al.*, 2013) may result from compensatory upregulation and that there seems to be nigrostriatal dopaminergic denervation in these patients.

We have reported post-mortem brain data in one asymptomatic and two symptomatic cases with GTP

cyclohydrolase 1-deficient DOPA-responsive dystonia, in whom substantially decreased levels, not only of tetrahydrobiopterin but also of neopterin, were confirmed in the brain (Furukawa *et al.*, 1999, 2002); the biochemical hallmark of GTP cyclohydrolase 1 deficiency is reduction of both pterins (Opladen *et al.*, 2012; Furukawa *et al.*, 2013). In these cases (including one patient who developed parkinsonism during adulthood), in marked contrast to patients with Parkinson’s disease, striatal levels of DOPA decarboxylase protein, the DAT (<sup>3</sup>H-WIN 35428 binding), and the vesicular monoamine transporter (<sup>3</sup>H-dihydrotrabenazine binding) were not decreased, indicating that nigrostriatal dopaminergic terminals are preserved in GTP cyclohydrolase 1-deficient DOPA-responsive dystonia. The post-mortem brain observations are consistent with *in vivo* findings in PET and SPECT literature on this autosomal dominant DOPA-responsive dystonia, including the reports of normal striatal <sup>18</sup>F-fluorodopa uptake in our autopsied cases (Furukawa *et al.*, 2013) as well as the reports of normal DAT and <sup>18</sup>F-fluorodopa PET or DAT SPECT imaging in patients with adult-onset parkinsonian phenotype (Nygaard *et al.*, 1992; O’Sullivan *et al.*, 2001; de la Fuente-Fernández *et al.*, 2003; Kang *et al.*, 2004; Lee *et al.*, 2009). Examinations of <sup>18</sup>F-fluorodopa PET and DAT SPECT revealed no abnormalities, even in more severely affected patients with tetrahydrobiopterin deficiency (i.e. autosomal recessive sepiapterin reductase deficiency) (Lee *et al.*, 2009; Friedman *et al.*, 2012).

There may be two types of adult-onset parkinsonism in GTP cyclohydrolase 1-deficient DOPA-responsive dystonia pedigrees. One is ‘benign’ parkinsonism due to a phenotypic expression of autosomal dominant DOPA-responsive dystonia (Nygaard *et al.*, 1992; O’Sullivan *et al.*, 2001; de la Fuente-Fernández *et al.*, 2003; Kang *et al.*, 2004; Furukawa *et al.*, 2013). Patients with this type of parkinsonism respond markedly to low doses of levodopa and, when treated with optimal doses, remain functionally normal for a long period of time without developing motor adverse effects of chronic levodopa treatment (motor response fluctuations and levodopa-induced dyskinesias); although patients with relatively severe GTP cyclohydrolase 1 deficiency may manifest dyskinesias at the initiation of levodopa therapy, such dyskinesias subside following dose reduction and do not reappear with later slow dose increment (Furukawa *et al.*, 1998, 2013). Intriguingly, one of the 11 *GCH1* variants (c.334A>G; p.T112A) reported by Mencacci *et al.*, (2014) has been found recently in two brothers with clinical diagnosis of Parkinson’s disease showing a DAT SPECT scan without evidence of dopaminergic deficit (SWEDD) (Cilia *et al.*, 2014). Thus, there is a possibility that SWEDD in some parkinsonian patients might be caused by a heterozygous *GCH1* mutation, whereas a pathogenic role of the T112A in humans remains undetermined (Cilia *et al.*, 2014; Mencacci *et al.*, 2014). An age-related decline of striatal tetrahydrobiopterin during adulthood could contribute to adult-onset ‘benign’ parkinsonism (Furukawa and Kish, 1998). The other type is ‘neurodegenerative’ parkinsonism, including Parkinson’s disease, in *GCH1* mutation carriers (Mencacci *et al.*, 2014). According to Mencacci *et al.* (2014), two of the four adult-onset parkinsonian patients (all of whom showed abnormal DAT SPECT imaging in their DOPA-responsive dystonia families) required increasing doses of levodopa and developed levodopa-induced dyskinesias during chronic levodopa therapy. In another parkinsonian patient associated with a heterozygous missense *GCH1* mutation, biochemical analysis demonstrated low tetrahydrobiopterin and normal neopterin in CSF. This pattern of pterin changes can be observed in the brain and CSF of Parkinson’s disease but not of GTP cyclohydrolase 1 deficiency (Furukawa *et al.*, 1999, 2013; Opladen *et al.*, 2012), suggesting that parkinsonism in this patient may be caused by nigrostriatal dopaminergic degeneration but not by a considerable defect in dopamine biosynthesis due to haploinsufficiency of *GCH1*.

As described, one of the reliable clinical distinctions between these two types of adult-onset parkinsonism is the subsequent occurrence of motor complications of chronic levodopa treatment in ‘neurodegenerative’ parkinsonism. Nevertheless, this is a retrospective difference. From a therapeutic point of view, an investigation of the

nigrostriatal dopaminergic terminals by DAT SPECT (SPECT is usually more available than PET) before starting levodopa administration appears to be important in adult-onset parkinsonian patients from GTP cyclohydrolase 1-deficient DOPA-responsive dystonia pedigrees; in this case, interpretation of the result should be cautious as DAT SPECT imaging has been reported to overestimate nigrostriatal terminal loss (Tatsch, 2002). If ‘Parkinson’s disease-like nigrostriatal dopaminergic denervation’ is detected by DAT SPECT in these parkinsonian patients, especially in early-onset patients, it may be better to start with a dopamine agonist to avoid motor complications of chronic levodopa therapy as much as possible. We are confident that findings of genetic and/or environmental factors which can modulate the outcome of *GCH1* mutations will, in addition to providing clarification of the mechanisms of ‘benign’ and ‘neurodegenerative’ parkinsonism in GTP cyclohydrolase 1-deficient DOPA-responsive dystonia families, provide exciting information regarding a role of the nigrostriatal dopaminergic terminal function in the pathogenesis of levodopa-induced dyskinesias.

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