Case Reports in Neurology

Case Rep Neurol 2015;7:84–89

DOI: 10.1159/000381827
Published online: April 14, 2015

1662–680X/15/0071–0084$39.50/0
www.karger.com/crn

Familial Hemiplegic Migraine Type 1 Associated with Parkinsonism: A Case Report

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Key Words
Familial hemiplegic migraine type 1 · Parkinsonism · *CACNA1A* · Spinocerebellar ataxia type 6 · Episodic ataxia type 2

Abstract
Familial hemiplegic migraine type 1 (FHM1), episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) are allelic disorders caused by mutations in the *CACNA1A* gene on chromosome 19p13. It is well described that FHM1 can present with cerebellar signs, but parkinsonism has not previously been reported in FHM1 or EA2 even though parkinsonism has been described in SCA6. We report a 63-year-old woman with FHM1 caused by an R583Q mutation in the *CACNA1A* gene, clinically presenting with migraine and permanent cerebellar ataxia. Since the age of 60 years, the patient also developed parkinsonism with rigidity, bradykinesia and a resting tremor. An MRI showed a normal substantia nigra, but a bilateral loss of substance in the basal ganglia, which is in contrast to the typically normal MRI in idiopathic Parkinson's disease. Dopamine transporter (DAT) imaging with single-photon emission computed tomography demonstrated a decreased DAT-binding potential in the putamen. We wish to draw attention to FHM1 associated with parkinsonism; however, whether the reported case is a consequence of FHM1 being allelic to SCA6, unknown modifiers to the specific R583Q *CACNA1A* mutation or idiopathic Parkinson's disease remains unanswered.

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Introduction

Familial hemiplegic migraine type 1 (FHM1) is often associated with cerebellar signs, which may be permanent in 20% of all FHM patients and present in 40–50% of FHM1 cases [1, 2]. We present a case with FHM1 caused by an R583Q mutation in the *CACNA1A* gene with cerebellar ataxia, and also parkinsonism, a feature which has not previously been reported in association with FHM1.

Case Presentation

This 63-year-old woman is a member of a family with FHM1 and cerebellar ataxia. Due to significant ataxia, more family members were tested with negative results for spinocerebellar ataxia (SCA) due to expanded trinucleotide repeats in the genes causing SCA1, SCA2, SCA3 and SCA6 in the 1990s. During a subsequent family study, a heterozygous R583Q mutation in the *CACNA1A* gene was identified as causative of the autosomal dominantly inherited hemiplegic migraine and cerebellar ataxia in the family. In that study, the family was found to comprise 11 members with hemiplegic migraine, of whom 10, including our patient, had associated slowly progressive cerebellar ataxia, with confirmed cerebellar atrophy on MRI in 3 individuals and by CT scan in 1 patient (family 6034 in [3]). By history, the patient's deceased mother also had both hemiplegic migraine and parkinsonism, but she was never medically examined or diagnosed.

Since early childhood, the patient had a poor balance, and from the age of 13 years, migraine with aura symptoms described as photosensitivity, scintillating scotomas, unilateral hemiparesis and dysphasia occurred. The migraine attacks followed the menstrual cycle but diminished after menopause, and persisting aura symptoms beyond 3 days never occurred. During the previous 2–3 years, the patient experienced a progressive gait instability, stiffness and right-sided resting tremor. A neurological examination revealed hypomimia, bilateral gaze-evoked horizontal nystagmus, normal saccades, right-sided, slight 'cogwheel' rigidity, bradykinesia and resting tremor. Moreover, finger tapping and hand diadochokinesia were reduced in speed, amplitude and regularity, predominantly on the right side. There was a slight ataxia of the limbs and a broad-based gait with forward-flexed posture and a reduced swing of the right arm. Treatment with selegiline and atenolol have reduced the tremor slightly, but otherwise had limited effects on the extrapyramidal symptoms.

The patient carried the heterozygous R583Q mutation in the *CACNA1A* gene, and a molecular genetic analysis excluded expanded trinucleotide repeats in the genes for SCA1, SCA2, SCA3 and SCA6 as causative. An MRI showed a decreased signal on T1-weighted MRI, an increased signal on T2-weighted MRI and an increased self-diffusion in the globus pallidus bilaterally. Moreover, the MRI revealed enlarged Virchow-Robin spaces and cerebellar atrophy most pronounced in the vermis, a normal substantia nigra (SN), and only a few unspecific white matter lesions. After 1 year, the MRI was repeated without any signs of progression (fig. 1, fig. 2), and additionally, short echo time MR spectroscopies from volumes of interest in occipito-parietal white matter and mid-occipital grey matter were found to be normal. Three consecutive dopamine transporter SPECT scans (DAT-SPECT) were acquired from 2011 to 2014. A decreased DAT-SPECT density in the striatum most prominent on the left side, and a reduced putamen/caudate ratio bilaterally, were demonstrated (fig. 3). The changes were relatively stable, and the DAT density was only reduced by 12% from 2011 to 2014.

Discussion

FHM is a rare, autosomal, dominantly inherited subtype of migraine with aura. Attacks are characterized by the presence of hemiparesis or hemiplegia, typically in association with other aura symptoms such as hemianopic scintillating scotomas, unilateral paraesthesias, numbness and dysphasia. FHM is classified into 3 types: FHM1, which is caused by *CACNA1A* mutations on chromosome 19p13, FHM2, caused by *ATP1A2* mutations on chromosome 1q21–23, and FHM3, caused by *SCN1A* mutations on chromosome 2q24 [1, 3]. Episodic ataxia, type 2 (EA2) and SCA6 are allelic disorders to FHM1 caused by mutations in the *CACNA1A* gene on chromosome 19p13 encoding the neuronal P/Q-type voltage-gated calcium channel [4, 5].

Besides migraine and hemiplegia, FHM1 is associated with a broad spectrum of clinical features that varies among families. Cerebellar symptoms may be episodic or a progressive feature of the clinical presentation and can be permanent in FHM1 families, some members of which also develop cerebellar atrophy on MRI [1, 4]. Most likely, these cerebellar features may be attributed to FHM1 being allelic to EA2 and SCA6, all caused by *CACNA1A* mutations.

EA2 presents clinically with attacks of generalized ataxia with or without migraine, whereas SCA6 is associated with a CAG repeat expansion in the *CACNA1A* gene and is clinically characterized predominantly by adult-onset cerebellar ataxia, dysarthria and oculomotor disturbances consisting of gaze-evoked nystagmus, gaze paresis and diplopia. MRIs of the brain in patients with SCA6 reveal cerebellar atrophy [6].

Earlier, SCA6 was considered an almost pure cerebellar ataxia, but several reports have indicated that patients with SCA6 also manifest a wide spectrum of non-cerebellar system involvement such as autonomic dysfunction, pyramidal and extrapyramidal signs. Reported extrapyramidal findings include dystonia, facial impassivity, monotonous soft voice, short-stepped gait, reduced arm swing, rigidity, bradykinesia, retropulsion and resting tremor, either alone or in variable combinations. Based on this, it has been proposed that neurodegeneration or neuronal dysfunction in SCA6 not only occurs in the cerebellum, but also involves the substantia nigra producing signs of parkinsonism in rare cases [5–9].

Our patient was diagnosed with FHM1 including a clear cerebellar involvement, and in addition, she also developed a right-sided hemi-parkinsonism. Parkinsonism has been associated with SCA6, but not previously described in relation to FHM1. However, the literature only provides a small number of reported FHM1 patients presenting with a heterogeneous and not clearly defined R583Q phenotype [10]. We therefore hypothesize that FHM1 may be associated with parkinsonism as a consequence of being allelic to SCA6 and/or unknown modifiers in relation to the specific R583Q *CACNA1A* mutation.

Another possible explanation could of course be that our patient developed idiopathic Parkinson's disease (iPD), unrelated to her FHM1 disease. Conventional MRI scans of iPD patients do not provide highly specific findings, but they may show changes suggestive of iPD-like midbrain volume losses, narrowing of the pars compacta in SN on T2-weighted sequences, and the loss of normal SN hyperintensity on T1-weighted sequences [11]. In contrast, our patient's MRI showed a clear visual symmetric bilateral loss of substance in the basal ganglia, enlarged Virchow-Robin spaces, normal SN and no typical appearance of iPD, which indicates another pathogenesis than iPD and supports the hypothesis of parkinsonism being related to FHM1. Migraine can cause mild ischaemic cerebrovascular deficits in rare cases [12], but the history is not consistent with the International Headache Society criteria for migrainous cerebral infarction [13], and the MRI shows no signs of vascular infarction.

Extrapyramidal signs and reduced striatal DAT-SPECT density in SCA6 patients have previously been reported [5, 9], while DAT-SPECT scans of FHM1 patients, to our knowledge,

have not been published before. In our patient, the DAT availability in her putamen was significantly reduced compared to age-matched healthy volunteers. Interestingly, repeated DAT-SPECT with an interval of 3 years showed only a slight yearly decrease in DAT availability (12% in 3 years) comparable to test-retest variability [14]. This is less than the expected yearly reduction of approximately 8% in DAT availability in patients with iPD and suggests a different pathophysiological mechanism [15].

Previous studies have indicated that P/Q-type voltage-gated calcium channels are involved in the regulation of dopamine release from dopaminergic neurons in the substantia nigra [16]. It is therefore reasonable to argue that dysfunction of the calcium channels may influence the frequency of dopaminergic secretion events which may produce signs of parkinsonism. Other studies have shown that functional alterations in calcium channels result in cell death of cerebellar Purkinje cells, which may also be a possible pathophysiological mechanism in dopaminergic cells [17].

FHM1, EA2 and SCA6 are all allelic disorders with clinically related features. Parkinsonism has been reported as part of SCA6, and we suggest that parkinsonism may also be part of the FHM1 clinical spectrum as a consequence of being allelic to SCA6 and/or unknown modifiers in relation to the specific R583Q *CACNA1A* mutation. FHM1 mutations might therefore be considered in cases with the atypical presentation of parkinsonism in addition to migraine and ataxia.

Disclosure Statement

The authors declare that they have no competing interests.

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Fig. 1. Sagittal T2-weighted MRI sequence of the FHM1 case. The MRI sequence reveals a cerebellar atrophy most pronounced in the vermis.

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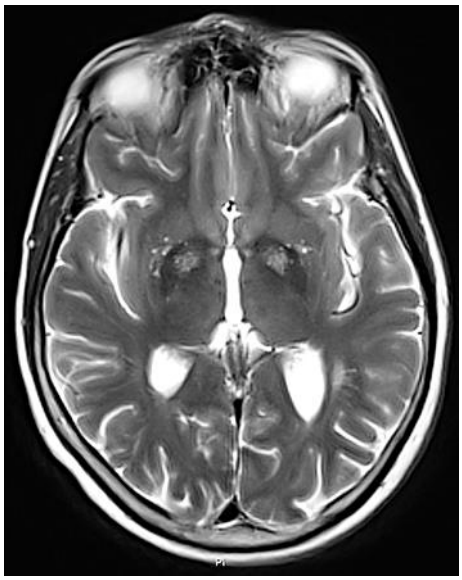

Fig. 2. Axial T2-weighted MRI sequence of the FHM1 case showing an increased signal of the globus pallidus bilaterally. Moreover, the MRI reveals enlarged Virchow-Robin spaces and only a few unspecific white matter lesions.

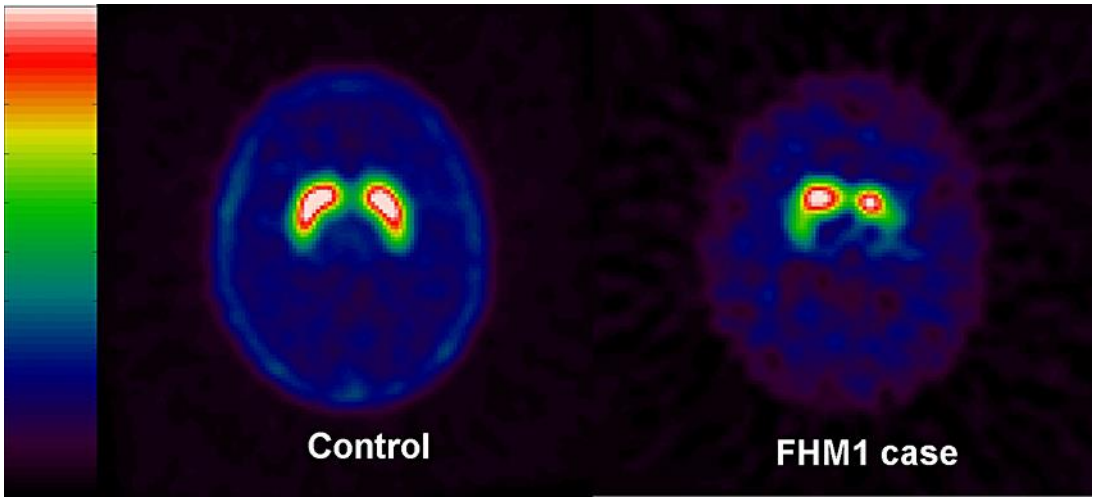

Fig. 3. SPECT imaging of DAT. The figure shows images of [^{123}I]FP-CIT binding to DAT in a healthy control (left) and in the FHM1 case. DAT availability in the striatum, i.e., the ratio of specifically bound radioligand to that of non-displaceable radioligand, was severely reduced bilaterally. The reduction in DAT availability was most prominent in the putamen on the left side (approx. 39% in of the value expected in a group of age-matched controls).