Pantothenate Kinase-Associated Neurodegeneration: Novel Mutations in the *PANK2* Gene in an Argentinean Young Woman

Neurodegeneration with brain iron accumulation (NBIA) refers to a heterogeneous group of disorders.[1–3] The pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive disorder caused by defective iron metabolism associated with mutations in the pantothenate kinase 2 (*PANK2*) gene on chromosome 20p13–p12.3.[3,4]

The "classic" PKAN phenotype is characterized by early onset, rapid progression, dysarthria, pigmentary retinopathy, and severe extrapyramidal signs. In the "atypical" phenotype onset occurs in the second decade of life with neurobehavioral signs, speech difficulties, anarthria, aphonia, less severe extrapyramidal signs, incontinence, and a more variable progression.[1] In both cases, T_2-weighted magnetic resonance imaging (MRI) of the brain shows the typical "eye-of-the-tiger" sign.

Patient IV-1: Proband. This 27-year-old woman was the first of three children born to a healthy, non-consanguineous Argentinean couple. The family history was positive for involuntary movements and early cognitive impairment in one member from the paternal line (Patient II-4) and severe diurnal somnolence on the maternal line (Patients II-1 and III-1; Fig. 1A).

The antenatal and perinatal history of the patient was relevant because of preeclampsia, prematurity, and delivery with low birth weight (1,750 g). At the age of 3, loss of visual acuity was noticed; two years latter, a diagnosis of retinitis pigmentosa was performed. In the next two years, she progressed to gait impairment, postural instability, and recurrent falls. On teenage, she suffered personality splits, progressive behavioral and obsessive disorders, and psychotic crisis with two suicidal attempts at age 11 and 14, respectively. By age 17, she developed dysphagia, echolalia, palilalia, and a severe dysarthria. She finalized the high school with a low performance. On the last four years, progressive cerebellar and extrapyramidal signs were evident.

On December 2007, the patient presented two partial seizures secondarily generalized and, on January 2008, she was admitted in our center. The patient was severely handicapped and able to perform only a few steps with assistance. The neurological examination showed a young woman with cognitive impairment, oftalmoparesis, severe dysarthria, extrapyramidal rigidity, dystonia involving the four limbs, ataxia, and spasticity. There were frequent episodes of aspiration pneumonia. Her parents, however, refused a gastro-jejunostomy. A T_2-weighted brain MRI showed the "eye-of-the-tiger" sign (Fig. 1B). Extensive biochemical blood and urine investigations including serum copper, ceruloplasmine levels, and plasma lipoproteins were normal. Presence of acanthocytosis was negative. Several symptomatic treatments were provided but only low doses of levodopa/carbidopa (250/25 mg/day) provided a transient benefit.

After signed informed consent, DNA was isolated from peripheral blood of the proband, and the various regions of the *PANK2* gene were amplified by PCR, sequenced, and analyzed as described elsewhere.[4] These sequence analyses revealed two different novel mutations in the *PANK2* gene: c.308G>A (p.W103X) corresponding to a premature stop codon and c.325G>A (p.G109S) which conceptually replaces amino acid glycine 109 by serine (Fig. 1C). Molecular analyses of either the parents of the patient or additional members of the family were not possible.

The finding of two novel mutations on the *PANK2* gene in a patient with a particular neurological phenotype, support current concepts about the wide clinical phenotypic heterogeneity of PKAN.[1] Among previously identified mutations in the *PANK2* gene, c.1231G→>A is the most frequent and accounts for 25% of disease-associated *PANK2* alleles.[1] To our knowledge PKAN patient carrying mutations c.308G>A (p.W103X) or c.325G>A (p.G109S) have not been reported.[1–3,5] The resemblance of the clinical presentation of the patient to reported PKAN cases strongly suggests a pathogenic role for these novel *PKAN2* mutations. Either of these mutations, or their simultaneous presence in the patient, appears to cause an unusual "mixed" clinical phenotype with early visual symptoms as reported in the "classic" form, but slow progression, seizures, behavioral, psychiatric, and cognitive manifestations, likely to the "atypical" phenotype.[1,3]

In summary, the patient reported here shows a peculiar PKAN clinical phenotype probably based on new mutations identified in the *PANK2* gene. We hypothesize that these mutations lead to PANK2 protein instability and/or reduced enzymatic activity.

The large phenotypic variability in PKAN patients highlights the value of molecular investigation to distinguish PKAN with *PANK2* gene mutation from other NBIA.[5–7] These studies would also allow identifying novel pathogenic mutations and contributing to the knowledge of the pathophysiology of these diseases.

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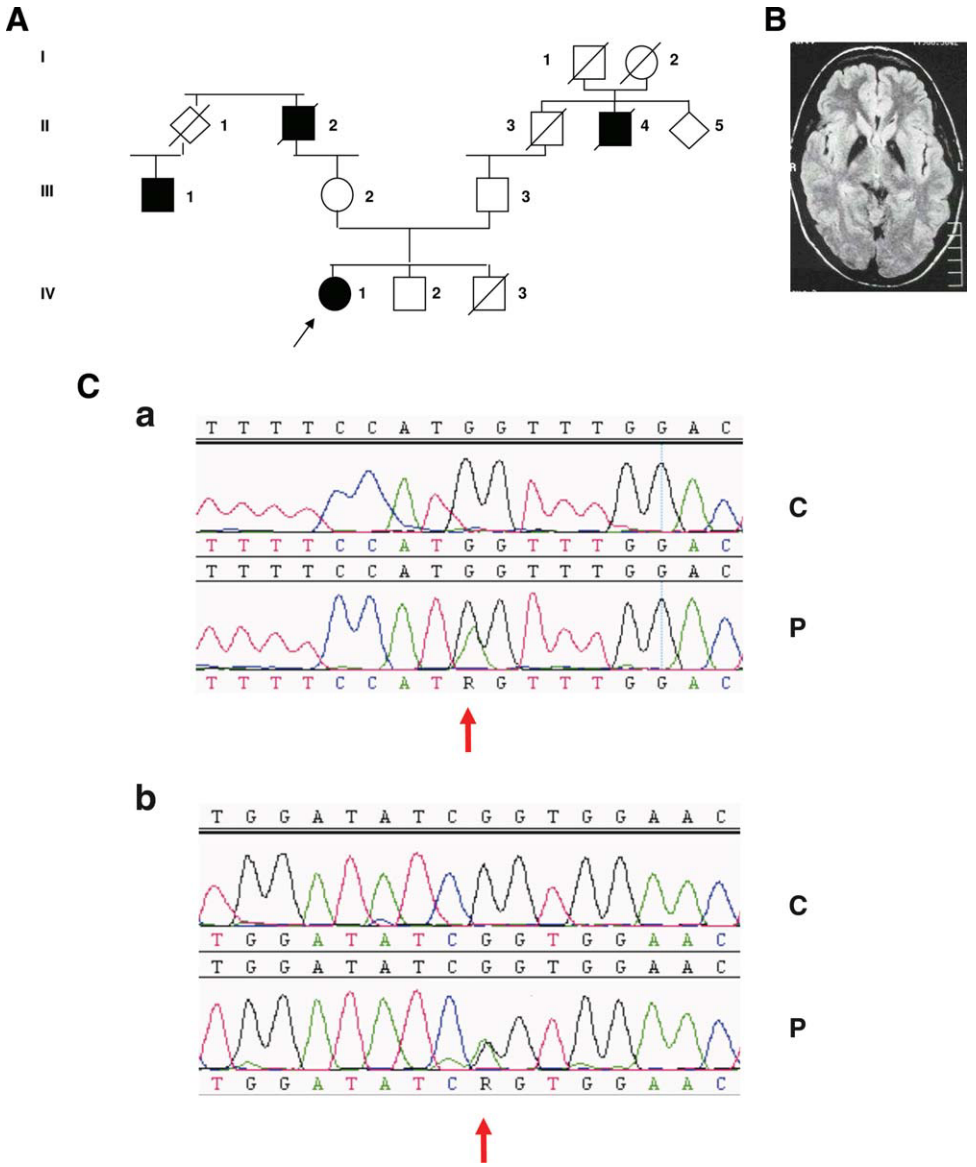

FIG. 1. PKAN in Argentina. **A**: Argentinian PKAN pedigree. **B**: Axial section of T2-weighted MRI scan of the patient IV-1 (see Fig. 1A) shows bilateral "eye of the tiger sign." **C**: Mutations c.308G > A and c.325G > A in patient IV-1. Panels show capillary electrophoresis electropherograms of DNA samples from a control individual (top rows: C) and patient IV-1 (botton rows: P). Panel a: mutation c.308G>A. Panel b: mutation c.325G>A. Vertical arrows indicate the position of the respective nucleotide changes. Both mutations are potentially pathogenic and have not been previously described. The mutation c.308G>A generates a premature stop codon (p.W103X), while the mutation c.325G>A is a misssense mutation (p.G109S). The same amino acid residue (G109) is mutated in another PANK patient (c.326G > T, p.G109V; see Ref. 3). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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Drug-Induced Cranial Myoclonus

Video 

Drug-induced myoclonus is an under-appreciated problem in the area of movement disorders. Many patients with myoclonus are taking a large number of medications and dissecting out which agent might be the culprit is often a very challenging problem, in part because many cannot readily be tapered as they treat important medical conditions. This is additionally complicated by the broad differential diagnosis of myoclonus, which can require extensive work-up for an underlying brain disorder. Here, we present two cases of cranial myoclonus, mistaken for stuttering, that were caused by amandatine and bupropion, respectively, and discuss the possible mechanisms of action underlying this abnormal movement.

Case 1 was a 63-year-old man who was seen in clinic for a 6 year history of progressive parkinsonism. He presented with bilateral upper extremity resting tremor, right-sided rigidity and postural instability with early falls. He was maintained with daily dosages of 800 mg levodopa (L-dopa) and 4.5 mg pramiprexole that provided only mild improvement. His rigidity progressed to become markedly axial, his tremor subsided, his balance worsened to cause increased falls, and he developed urinary incontinence. Imaging was unhelpful. A confident diagnosis could not be made, but progressive supranuclear palsy (PSP) and multiple system atrophy were entertained. Amantadine was started for postural instability. Several months after being maintained on a dose of 100 mg TID, he experienced a subacute onset of "stuttering" and at times mild difficulties chewing food ("I can not control my mouth"). On examination, he demonstrated resting and action myoclonus in his lower face that interfered with speech to give rise to "stuttering" (Video segment 1A). To exclude a contribution of amantadine to these symptoms, the medication was discontinued with complete resolution of the "stuttering" (Video segment 1B), indicating that the myoclonus was not a symptom of the progressive disease. Over the next 2 years, the patient developed supranuclear vertical gaze palsy and midbrain atrophy on MRI, supporting a diagnosis of probable PSP.

Case 2 was a 69-year-old woman who was referred for "stuttering." This complaint started 2 years earlier and worsened gradually to the point that she had difficulties communicating effectively. She had been avoiding social gatherings, because nervousness increased her stuttering. Medical history was notable for long-standing depression and anxiety, for which she had been treated with various antidepressants. At the time of presentation, she was on citalopram (60 mg po qd) and bupropion (200 mg po qd). She had been recently treated for breast cancer with a left mastectomy and six courses of chemotherapy. Stuttering began several months after the initiation of chemotherapy. Other medications included risperidone (0.5 mg po qd), clonazepam (0.5 mg po up to 6 times per day), and rosuvastatin. Risperidone withdrawal and a trial of L-dopa had not improved the stuttering. Examination showed action myoclonus of the lower face. Talking increased the myoclonic activity and interrupted the fluency of her speech (Video segment 2A). Given the history of breast cancer and concerns about a neurodegenerative disease, MRI of her brain was performed and was unremarkable. Her psychiatrist was asked to reduce the antidepressants as much as possible to assess whether medications contributed to her myoclonus. Tapering of citalopram did not reduce the "stuttering". In contrast, after citalopram was reintroduced and bupropion tapered off, her speech difficulties resolved completely (Video segment 2B).

A thorough literature review of drug-induced cranial myoclonus revealed only one report, in which a patient was found to have "vocal" myoclonus in the context of amantadine administration.[1] Review of this paper's video, however, demonstrates that the myoclonus clearly relates to the attempt to speak, similar to what is seen in our patients. Hence, the term "vocal" myoclonus is confusing and may be more appropriately replaced by cranial myoclonus as well. Our Case 1, presenting as "stuttering", is only the second case of action myoclonus of the lower face caused by amantadine. Case 2, to our knowledge the first report of action myoclonus of the lower face due to bupropion, shows that this complication is not restricted to one drug or drug class alone. Similar speech-related action myoclonus can occur with other disorders, for example the Lance Adams syndrome.[2] However, rarely if ever is the problem isolated to the cranial musculature interfering exclusively with speech. Recently, a case clinically very similar to ours was reported as a consequence of varicella encephalitis.[3]

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