LESSON OF THE MONTH

Wilson's disease presenting in a family with an apparent dominant history of tremor

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Abstract

A patient with Wilson's disease is described who presented with dystonic tremor in a family with an apparent dominant history of tremor. Subsequent investigation showed that the patient's mother had essential tremor, with molecular analysis of the ATP7B gene excluding the possibility of pseudodominant inheritance. This case highlights the importance of considering the possibility of Wilson's disease in every young patient with a movement disorder, even where the clinical picture does not suggest a recessively inherited disorder.

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Wilson's disease is an autosomal recessive disorder of biliary copper excretion due to mutations in the ATP7B gene on chromosome 13, with an estimated prevalence of 1 in 30 000. The prognosis is invariably poor if the diagno-

sis is missed, yet it can present with a wide range of neurological, hepatic, or psychiatric features. Some 40%–50% of patients with Wilson's disease present neurologically, with tremor being the initial symptom in about half such cases—either as an action, resting, or postural tremor.¹ We describe a patient in whom an apparent dominant history of tremor proved misleading, but following the axiom “consider Wilson's in all young patients presenting with a movement disorder” led to the correct diagnosis. This emphasises the importance of considering the possibility of Wilson's disease, even where the family history does not initially seem to be compatible with a recessive disorder.

The proband (III:1, see fig 2) was an 18 year old right handed white college student reading art and design. Over the past 2 years, he had noticed an intermittent asymmetric hand tremor which worsened with action, that had progressively worsened such that his drawing had deteriorated. He had also developed a “no-no” head tremor which was worse in the morning, and some dystonic posturing of his

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Figure 1 Kayser-Fleischer ring in III:1 before treatment (fig 1 A) and after treatment with antichelation therapy for 15 months (fig 1 B and 1 C). Note the partial clearance of the Kayser-Fleischer rings on the inferior aspect and persistence on the superior aspect of the cornea (fig 1 C and fig 1 B respectively).

left hand, such that drawing was becoming problematic. He also complained of numbness along the ulnar aspect of his left hand. In the lower limbs, he had noted an intermittent right foot tapping. He reported that his mother (II:2) had a similar hand tremor with no foot tremor and that his maternal grandmother (I:2) had a hand and foot tremor. His general practitioner had treated him with propranolol with partial benefit. At the initial clinic visit, he had some stimulus sensitive dystonic posturing of the right foot, particularly with pressure over the right foot. There was minimal postural tremor of his arms, and no evidence of dystonia in other limbs. There were no other extrapyramidal or pyramidal signs. No Kayser-Fleischer rings were initially noted on naked eye examination (by either of us).

As the precise diagnosis was unclear, other investigations were performed and the other affected family members were examined (a video of III:1 and II:2 is at http://medweb.bham.ac.uk/http/depts/clin_neuro/papers/jnnp/nicholl-etal.mov).

His plasma caeruloplasmin concentration was <0.06 g/l (normal 0.2–0.45 g/l), copper excretion was 806 µg/24 hours (normal <50 µg/24 hours) and head MRI showed areas of high signal on T2 weighted imaging in the basal ganglia, and to a lesser extent the mesencephalon, inferior cerebellar peduncles, and adjacent brain stem. Slit lamp examination demonstrated the presence of obvious Kayser-Fleischer rings which were, in retrospect, easily

visible on examination with the naked eye (fig 1 A). A liver biopsy showed changes compatible with Wilson's disease with increased hepatic copper content. Nerve conduction studies were normal, with no evidence of an ulnar neuropathy. His Kayser-Fleischer rings partially cleared with penicillamine and zinc therapy after 15 months treatment (slit lamp examination shown in fig 1 B and C) and he improved sufficiently to finish top of his class at college.

The proband's 54 year old mother (II:2) had had a history of a non-progressive predominantly postural tremor of both arms since her late teens. The tremor improved with alcohol. She was not on any treatment. Examination disclosed a postural tremor that worsened with action. There were no other neurological signs. The clinical diagnosis was of benign essential tremor.

The 86 year old grandmother (I:2), in fact, was neurologically normal with no evidence of tremor. She had no recollection of ever being symptomatic with tremor. All other family members were normal on examination. Copper studies and slit lamp examination were normal in all first degree relatives of the proband.

Haplotype analysis was performed using three common microsatellite markers for the ATP7B gene—namely, D13S314, D13S301, and D13S316. For all of them, we used the same polymerase chain reaction (PCR) conditions: 33 cycles of 94°C for 20 seconds, 62°C for 30 seconds, and 72°C for 25 seconds. For each marker, we used one fluorescently labelled primer in the PCR. To define the exact size of the fragment detected by the respective marker, an ABI Prism 310 Genetic Analyzer and Genescan Software were used. For comparison with the numbering of haplotypes according to convention,² we have received and haplotyped samples provided by D Cox (University of Alberta, Edmonton, Canada). As shown in fig 2, III:1 was a compound heterozygote (H1069Q/?), his father, mother, and brother were heterozygotes (II:1, H1069Q/wt; II:2, ?/wt; III:2, H1069Q/wt respectively where ? is an unidentified mutation). I:2 was homozygous wild-type (wt/wt). Direct sequencing of the coding regions (exons 8 and 15, responsible for ~25% of mutations) of the ATP7B gene has, to date, failed to identify the novel mutation.

The co-occurrence of essential tremor, the commonest movement disorder, with Wilson's disease has not previously been reported although other forms of dystonia have been described.³ The apparent dominant history of tremor in this family misled us initially into considering Wilson's disease as not being very likely. Pseudodominant inheritance of Wilson's disease has rarely been reported,⁴ but this was excluded both via the haplotyping data, and as the phenotypic features in the mother are more in keeping with essential tremor. Although the H1069Q allele seems to be the most common mutation in patients of northern and eastern European ancestry (with an allelic frequency of ~37%, but as high as 93% in Polish subjects), the molecular

Figure 2 Family pedigree

diagnosis of Wilson's disease is not straightforward as there are more than 190, usually rare, mutations.² None the less, haplotype analysis can provide a definitive method for establishing carrier status in first degree relatives as in subject III:2 (fig 2).

Finally, one recent study suggested that dystonic tremor is often misdiagnosed as essential tremor, even by neurologists³; thus it is vital that the possibility of Wilson's disease is considered in every patient under the age of 50 with a progressive movement disorder, even

where the family history does not suggest a recessive mode of inheritance.

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NEUROLOGICAL PICTURE

“The other” Babinski's sign: paradoxical raising of the eyebrow in hemifacial spasm

Joseph Babinski is famous for his description, in 1896, of the abnormal plantar reflex as an indicator of dysfunction in the pyramidal tract. After the works of Brissaud and Meige, his contribution to description of hemifacial spasm is much less well known.

He reported for the first time paradoxical syncinesis in hemifacial spasm in a lecture given at the Société Neurologique de Paris on 6 April 1905.¹ “The most singular is the following: when orbicularis oculi contracts and the eye closes, the internal part of the frontalis contracts at the same time . . . the eyebrow rises during eye occlusion . . . this set of occurrences is impossible to reproduce by will . . .”

From these observations, Babinski concluded that hemifacial spasm is neither the result of a psychological problem nor of a cortical lesion, but instead is due to a lesion that affects directly the facial nerve.

This “other” Babinski's sign can, occasionally, be useful in distinguishing hemifacial spasm from other craniofacial movement disorders.

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Figure 1 Left hemifacial spasm. Paradoxical raising of the eyebrow as the eye closes (the “other” Babinski's sign) (with permission).