Atypical parkinsonism

Ten steps to identify atypical parkinsonism

D J Burn

Credibility of the 10-step test in atypical parkinsonism

Like the England football team entering a major world championship, there is always the hope that a new test to differentiate Parkinson's disease from atypical parkinsonism will be successful. Unfortunately, and in keeping with the soccer analogy, several of these tests have often failed at the quarter final stage! In the paper by Abdo *et al*¹ (see p 1367), a remarkably simple clinical test is described that may be useful in making this differentiation. In this test, the patient is asked to take 10 consecutive tandem steps along a straight line without walking aids or support. An abnormal test is defined by one or more side steps while performing this task. In their cohort of 85 consecutively referred patients, 36 patients had Parkinson's disease, whereas the other 49 had a variety of "atypical" parkinsonian conditions, including multiple system atrophy (n = 24), progressive supranuclear palsy (n = 4) and vascular parkinsonism (n = 14). Overall, an abnormal tandem gait test differentiated Parkinson's disease from atypical parkinsonism with a sensitivity of 82% and a specificity of 92%.

In keeping with most clinical tests or investigations purported to differentiate Parkinson's disease from atypical parkinsonism, clinical diagnosis was regarded as the gold standard in this paper, thereby introducing potential circularity to the argument. Replicating the utility of the 10-step test in early, undifferentiated parkinsonism with longitudinal follow-up to definitive diagnosis (preferably with pathological confirmation) would be ideal, although it is difficult in practice. Encouragingly, however, only one patient having Parkinson's disease with disease duration of <3 years had an abnormal test, compared with 17 (85%) of 20 patients with atypical parkinsonism of similar disease duration.

Of further concern was the case mix and average age of the cohort; mean ages were 57.5 and 69 years for Parkinson's disease and atypical parkinsonism groups, respectively, whereas the frequency of atypical cases (57%) was much higher than would be encountered in most movement disorder clinics.² Thus, if we consider the positive predictive value (PPV) of the 10-step test, which is influenced by the relative prevalence of

the conditions, and derive this for two hypothetical clinical populations of 1000 patients—the first with 600 patients with Parkinson's disease and the second with 900 patients with Parkinson's disease—PPV for the first scenario is 87% and that for the second is 53%. In other words, in an arguably more "representative" clinical population, the PPV may not be as impressive as it first appears. Furthermore, because of the relatively young age of the Parkinson's disease group, potentially confounding effects of comorbidity on the patient's tendency to take side steps could have been overlooked.

The authors do not make extravagant claims for the utility of their test but recommend that it be included in the now legendary list of "red flags" for atypical parkinsonism, a term first proposed by Quinn.³ Advantages of the clinical test are its simplicity and speed of completion, and further evaluation is surely indicated. The 10-step test may not yet have passed the quarter final stage, but at least it is still in there with a chance!

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Paraneoplastic and genetic cerebellar ataxia

Understanding the physiopathology of paraneoplastic and genetic cerebellar ataxia

J Honnorat

Antibodies as diagnostic markers of ataxia

Despite their rarity, paraneoplastic syndromes have always intrigued neurologists. Several reasons explain this clinical and scientific interest. From a clinical point of view, the

discovery and characterisation of several paraneoplastic antibodies have allowed neurologists to diagnose puzzling neurological syndromes as paraneoplastic¹ and to more easily identify tumours that

are often small and occult.² From a scientific point of view, characterisation of the antigens recognised by paraneoplastic antibodies has led to the identification of proteins that are important for the functioning of the nervous system and tumorigenesis.³ In their paper,⁴ Sabater *et al* (see p 1359) report the identification of autoantibodies against protein kinase C (PKC) γ in a patient with paraneoplastic cerebellar ataxia (PCA). They identified these antibodies in only one patient, but the data suggest that PKC γ could have a role in PCA. Indeed, PKC is expressed at particularly high concentrations in the Purkinje cells of the cerebellum, where it is believed to have an important role in signal transduction and synaptic transmission.⁵ Missense mutations in the regulatory domain of PKC γ have

been identified as a cause of autosomal dominant cerebellar ataxia.⁶ Immunohistochemical studies on cerebellar tissue from an affected member of a family with PKC γ missense mutation showed reduced staining for both PKC γ and ataxin 1 in Purkinje cells, suggesting that there may be a common pathway for PKC γ and polyglutamine-related neurodegeneration.⁶ This hypothesis is also supported by the fact that in spinocerebellar ataxia type 1 (SCA1) transgenic mice, PKC γ degradation occurs before the onset of ataxia, suggesting that the loss of this protein is important for the Purkinje cell dysfunction observed in SCA1 patients.⁵ A link between paraneoplastic and genetic cerebellar ataxia is also illustrated by voltage-gated calcium channel antibodies (VGCC-Ab). VGCC-Ab, especially those directed against the P/Q type VGCC, are mainly associated with Lambert-Eaton myasthenic syndromes (LEMS),⁷ which are paraneoplastic in >70% of the patients. Studies have shown that the frequency of cerebellar ataxia in patients with LEMS is higher than that expected by chance, and that LEMS with ataxia is usually associated with cancer.⁸ VGCC-Ab against the P/Q type have also been found in patients with small cell lung cancer and PCA without LEMS,⁹ suggesting that VGCC

could be associated with some cases of PCA. P/Q type VGCCs are highly expressed in the cerebellum, and gene mutations coding for VGCCs have been identified as a cause of autosomal dominant cerebellar ataxia (SCA6).¹⁰ These data showed that PKC γ and P/Q type VGCCs could be associated with cerebellar ataxia as both paraneoplastic antigen and key mutated protein. From these observations, we can draw two conclusions: although PCA-associated antibodies have not definitively been proven to be pathogenic, they can be used as diagnosis markers to classify subtypes of cerebellar ataxia; although some paraneoplastic antibodies can be observed in only one or two patients, identification of the antigens may have important implications in the identification of key proteins, which could be associated with the neuronal injury of patients with sporadic or genetic cerebellar ataxia.

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Prevention of delayed cerebral ischaemia

Prevention of delayed cerebral ischaemia after subarachnoid haemorrhage

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Physiological abnormalities are a worthwhile target

Delayed cerebral ischaemia (DCI) affects more than one quarter of patients between 3 and 14 days after the onset of their aneurysmal subarachnoid haemorrhage, and accounts for about one third of patients who are dead or dependent as a result of the haemorrhage. Despite the importance of DCI, little can be done to prevent it: only calcium antagonists are supported by good evidence, and the effectiveness of nimodipine is modest (20 patients need to be treated to prevent one poor outcome).¹ Future hope is offered only by the window of

opportunity between subarachnoid haemorrhage and DCI onset, and sufficient clinical research interest in finding further interventions for the prophylaxis and treatment of DCI.

In trying to discover whether potentially modifiable physiological abnormalities are a worthwhile target for intervention to prevent DCI, the paper by Naidech *et al*² (p 1340) explores the association between cerebral infarcts on computed tomograms of the brain after aneurysmal subarachnoid haemorrhage and a physiological derangement score at the time of admission to hospital

(based on a patient's oxygenation, acidosis, glycaemic control and blood pressure). In contrast with the study that originally derived the physiological derangement score,³ the present study is small and retrospective, with an over-representation of subarachnoid haemorrhages that were severe or located in the posterior circulation. Furthermore, the study used a radiological marker of DCI rather than clinically important outcome data after discharge from hospital. The authors strove to identify cerebral infarcts due to vasospasm, but multivariate analysis found only clinical severity of subarachnoid haemorrhage and physiological derangement score to be associated with cerebral infarcts. However, the size of the study sample precluded the inclusion of other known determinants of DCI (such as prolonged duration of unconsciousness at onset of subarachnoid haemorrhage) and its design did not allow an analysis of the influence of endovascular or surgical treatment.

The study by Naidech *et al*² provokes many questions. Might alternative scoring systems using additional variables be better at predicting poor clinical outcome?⁴ Might altered physiology