Matters arising

Generalised dystonia, whispering dysphonia and Wilson's disease in members of the same family

Sir: We were interested in the recent report by Parker of generalised dystonia, whispering dysphonia and Wilson's disease occurring in members of the same family.[1] We have also seen a family where torsion dystonia and focal dystonia occurred in association with a rare metabolic disorder.

IW is now 28 years of age and suffers from typical torsion dystonia. Following a normal birth and delivery his early milestones were reported as being normal. At the age of 10 yr he developed inward turning of his left foot whilst walking, which subsequently progressed throughout his teens to generalised dystonia. Since the age of 20 yr his illness has been arrested and although moderately disabled, he is of normal intelligence. He has no other neurological deficit, fundoscopy is normal and there is no hepatosplenomegaly. Liver function tests, copper studies, examination of bone marrow histiocytes, CT brain scan and nerve conduction studies were normal. Although previously resistant to a variety of treatments he has experienced moderate benefit whilst taking benzhexol 27 mg daily.

IW has a younger brother who is normal and a sister who has been noticed to hold her head in an odd position, but no firm diagnosis has been reached. Another sister, following a normal birth and neo-natal period, presented at the age of 15 months with developmental delay and infantile spasms with a prominent startle response. A cherry red spot was found on fundoscopy. Her condition deteriorated with worsening epilepsy, enlarging head and neurological deterioration until she died in 1968 at the age of 2½ yr with a diagnosis of Tay-Sachs disease. Brain biopsy and post mortem examination were not performed.

The mother of IW has just come under our care at the age of 51 yr, with a 9 month history of pain in the neck, at first associated with a side-to-side tremor of the head. She subsequently developed a tendency of the head to be pulled back and to the right and has features typical of spasmodic torticollis. One year after the onset she has not developed dystonia elsewhere. There is an extensive family who are known to be well but a maternal cousin has been examined by us and also suffers from torsion dystonia. There is a history of consanguinity, in that the maternal grandparents of IW were first cousins.

Leucocyte lysosomal enzyme studies have been carried out on available members of the family. Alpha-neuraminidase, beta-galactosidase and beta-hexosaminidase A were all normal. However, IW his parents and one sibling all have low total hexosaminidase levels in plasma, 7·9 to 10·7 nmol/min ml (control 15·8) with a high percentage A component, 76 to 89% (control 68%). These findings are consistent with heterozygosity for GM2 gangliosidosis 0 variant and suggest that the diagnosis of the sibling who died in infancy was, in fact, Sandhoff disease. Lysosomal enzyme activities in the cousin with torsion dystonia were normal.

The occurrence of adult onset of focal dystonia in the parents of a patient with generalised torsion dystonia, although rare, is well recognised.[2] In our family the clinical picture was compatible with so-called idiopathic torsion dystonia. The relevance of low hexosaminidase levels and a family history of Sandhoff disease is uncertain. Hexosaminidase deficiency is subject to considerable phenotypic variation and although dystonia may occur, it has not been reported as a presenting feature.[3] Furthermore IW, and his mother were only carriers of the disorder and a maternal cousin who was subsequently identified as suffering from dystonia had normal hexosaminidase levels. The occurrence of dystonia and Sandhoff disease in the same family may, therefore, be due to chance association of two rare diseases, possibly related to the history of consanguinity.

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Patients with Parkinson's disease can employ a predictive motor strategy

Sir: Day *et al*[1] report that patients with Parkinson's disease can employ a predictive motor strategy. While other reports support this concept, an examination of their data suggests a different conclusion.

In their first experiment, patients and controls first tracked a pattern which they did not know was predictable and then one which they knew to be predictable. Tracking lag was used as a more direct measure of predictive movement than tracking error. However, the authors point out that these data were confounded by subjects' overcompensation for unanticipated changes in target direction, resulting in lag times below visual reaction time even when target movement was not known to be predictable. In some cases lag times took on negative values. These data are difficult to interpret and may not reflect predictive movement.

The key to finding was that both patients and controls improved their tracking lag times in a comparable fashion when the target path was known to be predictable. Unfortunately, the statistical analysis of these data relied on multiple *t* test comparisons. An ANOVA followed by *post hoc* comparisons is more appropriate. A simpler alternative would be to compare subjects' degree of improvement, operationalised as the difference between lag scores when the target is not and is known to be predictable. When this is calculated for each patient based on the data presented in table 1, a *t* test reveals that the controls showed significantly greater improvement ($t = 2{\cdot}28$, $p < 0{\cdot}01$). This would suggest that controls are better able to take advantage of the predictability of target movement. This is comparable to the findings of other investigators.[2–4]

Parkinsonians are capable of some degree of predictive movement, but quantitatively less than healthy people. Under some circumstances they may be able to accomplish predictive movements normally. Bloxham *et al*[5] showed that patients could generate a single "preprogrammed" predictive movement, in their case a circle, as well as controls. However, external cues are needed for patients to shift from one unit of movement to another, as is demanded by the sawtooth paths used by Flowers[2] and Stern *et al*.[3,4] In the present study, experience with a pattern allowed patients to improve their tracking performance, but not to the same degree as controls.

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Day *et al* reply

We thank Dr Stern for his comments and suggestions, but still believe that our conclusions hold. As stated in the final paragraph of the discussion to our paper, we think that the data show that patients with Parkinson's disease can and do adopt a predictive motor strategy when tracking a known target movement, but that they do so with less accuracy than normal subjects.

The issue of short-term prediction of unknown targets, which leads to tracking lags shorter than visual reaction times in both normals and Parkinsonians, is not the crucial point. It is the ability of Parkinsonians to reduce tracking lag closer to zero when the target movement is known that defines the use of a predictive motor strategy, and 11 of the 12 patients studied were able to do this. If, as suggested by Dr Stern, the patients and controls are compared by measuring the reduction in lag for each subject, then a t test does reveal a difference between the groups at the 5% level of significance ($t = 2{\cdot}29$, $p = 0{\cdot}33$ for a two-tailed test). ANOVA gives essentially the same result with a significant main effect of conditions ($F = 46{\cdot}88$, $p < 0{\cdot}001$) but not of groups ($F = 0{\cdot}05$, $p > 0{\cdot}05$) with a significant interaction between groups and conditions ($F = 5{\cdot}24$, $p = 0{\cdot}034$). However, it should be pointed out that strictly speaking a t test is not applicable to these data. The difference in variability of the two groups is large (variance ratio = 6·24) and the control data is skewed. The non-parametric Mann-Whitney test is more suitable but fails to reveal a difference between the groups ($U = 23$, $p > 0{\cdot}05$). Therefore, we believe that the present data are inconclusive on this point, and that this issue can be resolved only by further experimentation.

Our data show that even though a predictive strategy was used, the tracking *error* of the patient group did not improve as much as the control group. There are two possible ways of explaining this. Either the patients' tracking lag did not improve as much as controls', or, lag was reduced normally but the movements were more inaccurate. In contrast to Dr Stern, we favour the latter explanation for the following reasons: (1) The mean tracking lag of the patients was not statistically different from that of the controls in both the unpredictable and predictable conditions. (2) There was a correlation between the improvement in error and reduction in lag for the control subjects ($r = 0{\cdot}83$, $p < 0{\cdot}05$), but not for the patient group ($r = 0{\cdot}03$, $p > 0{\cdot}05$).

In conclusion, Dr Stern and we agree that patients with Parkinson's disease can adopt predictive movement, but less successfully than normal subjects.

Triphasic waves of metabolic encephalopathy versus spike-wave stupor

Sir: We disagree with the discussion that Yamamoto and Hosokawa give in their recent case report "Triphasic spike-wave stupor in portal-systemic encephalopathy."[1] They seem to confuse the EEG findings of triphasic waves seen in *metabolic* disturbances and spike-wave discharges seen in *epileptic* spike-wave stupor (also called absence status or petit mal status). This distinction has diagnostic and therapeutic importance.

Their patient was a 59-year-old woman presenting with episodic obtundation and a flapping tremor. Portal-systemic encephalopathy was diagnosed from laboratory and radiologic evidence of liver cirrhosis (including hyperammonaemia) and treated with lactulose and kanamycin. They concluded from EEG findings of "continuous bilaterally synchronous atypical spike-wave discharges of an epileptic nature" that the patient had spike-wave stupor secondary to portal-systemic encephalopathy.

A more accurate interpretation of the EEG (shown in the figure accompanying the case report) would be triphasic waves suggestive of a metabolic disturbance. Triphasic waves are medium to high amplitude, diffuse, frontally predominant, broad complexes consisting of a large positive (downward) sharp wave preceded and followed by small negative (upward) components.[2] These complexes last 0·15 to 0·25 seconds and recur singly or in serial trains about every 0·5 to 2 seconds. They are often superimposed on a background of asynchronous and bisynchronous slow waves. There is usually a tendency for fronto-occipital delay. Although rarely seen in degenerative processes or after anoxic episodes and head trauma, triphasic waves usually indicate toxic-metabolic encephalopathy, most commonly hepatic or renal. They are not epileptic phenomena.[3] There appears to be a limited correlation between blood ammonia levels and the triphasic wave pattern.[4] The treatment is usually correction of the underlying metabolic abnormality.

The spike-wave discharges accompanying spike-wave stupor are medium to high amplitude, generalised, predominantly fronto-midline, synchronous complexes (surface negative spike followed by surface negative slow wave). The morphology may be less regular than the spike-wave of typical absence seizures, and polyspikes may be admixed.[5] These repetitive spike-wave complexes fire rhythmically at a frequency of 2 to 6 Hz (usually 2·5–3·5 Hz).[6,7] The complexes may be continuous, or they may occur in repetitive bursts alternating with normal or near-normal background activity. A strong external stimulus may temporarily normalise the EEG.[5]

Spike-wave stupor (absence status) is an epileptic phenomenon clinically manifesting as a confused state lasting minutes to days. In most instances, it occurs as part of a pre-existing seizure disorder, usually absence seizures.[5,6] The treatment is usually by anti-epileptic medications.[9]

This case report illustrates how an EEG finding (triphasic waves) combined with appropriate laboratory and radiologic confirmation can differentiate the diagnosis of portal-systemic encephalopathy from other causes of episodic obtundation, including spike-wave stupor. Yamamoto and Hosokawa correctly point out that spike-wave stupor has occasionally been reported in patients without a previous seizure history. Rarely, the condition may be associated with acquired neurological disease (head injury, encephalitis, cerebrovascular disease)[6] or predisposing toxic-metabolic disturbances.[10] The same associations occur with typical absence seizures.[9]

The EEG distinction between triphasic waves and spike-wave discharges makes the EEG useful in ensuring that metabolic disorders and epileptic spike-wave stupor are each diagnosed and treated appropriately.

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