New mutations in Huntington’s chorea

Sir,

Shaw and Caro\(^1\) rightly point out that it is difficult to identify a person suffering from a new mutation for Huntington’s chorea because documentation is needed of: (1) parents and sibs who were healthy at late ages, (2) correct paternity, and (3) one or more affected children. However, an estimate of the proportion (p) of cases resulting from new mutations can be made simply from a modification of Haldane’s formula, namely: \(p = 1 - \) relative fitness. This formula assumes a state of equilibrium which is probably not present where there is widespread use of genetic counselling; therefore, estimates of p should be based on data obtained before genetic counselling.

Fitness is usually measured as the mean number of surviving children per gene carrying subject compared to that of controls. However, care has to be taken in measuring fitness in a disease where diagnosis and ascertainment are aided by the presence of an affected relative. The inclusion of such an affected relative in estimates of fitness is usually incorrect. It is clear that the affected parent of an index patient should not be included since he/she was selected by having at least one child, but it may not be so obvious that all of a sibship should be excluded if one of the affected persons was ascertained through an affected descendant.\(^2\) Indeed, it is possible that any patient ascertained partly because of a known affected relative leads to a biased ascertainment of families with above average fertility, and therefore it might be best to include only index patients and not their affected relatives when estimating fitness. Another point to be noted when estimating fitness of persons carrying the gene for Huntington’s chorea is that the early onset cases, who die before completing their reproductive period, should not be excluded, for this would lead to an estimate of fitness only for persons less mildly affected.\(^2\) A further point made by Reed and Neel\(^6\) was that the data in patients must be compared to population data and not to data provided by unaffected sibs, since the latter tend to have smaller families than persons without a family history of Huntington’s chorea.

Shaw and Caro\(^1\) list in table 1 some estimates of fitness for Huntington’s chorea, but some of these reports\(^3\)–\(^5\) did not make it clear which affected relatives were used, and some\(^6,6\) compared the fertility of patients to their unaffected sibs. Reed and Neel\(^2\) and Wendt and Drohm\(^7\) were aware of the problems in estimating fitness and their estimates of 0.81 and 0.95 are more likely to be correct than the others listed in the table. These two figures suggest that the proportion of new mutants among all cases of Huntington’s chorea is likely to be about 10%.

Shaw and Caro\(^1\) argue that some patients with the phenotype of Huntington’s chorea do not possess the gene and that therefore their descendants are not at risk for developing the same disease. However, if allowance is made for late onset of disease, analysis of the segregation ratio among children of Huntington’s chorea patients shows no significant difference from the 1:1 ratio expected if all cases (and not just a proportion) possessed an autosomal dominant gene.\(^3\) Secondly, in contradistinction to Shaw and Caro’s assertion, I believe that the clinical picture of Huntington’s chorea, once neurological signs have appeared, is so distinctive that it is rare for a neurologist to make an incorrect diagnosis of the condition. It is difficult to imagine what other disorder could give rise to the triad of dementia (which is unlike that seen with the other presenile dementias), chorea, and other features of extrapyramidal pathology, although one patient has been reported with these signs who at necropsy was found to have widespread cerebral atherosclerosis, cerebral atrophy, and bilateral lacunar infarcts of the corpus striatum.\(^9\) The misdiagnosis rate of 29 to 40% quoted by Shaw and Caro\(^1\) refers mainly to patients with Huntington’s chorea who were initially diagnosed as suffering from other conditions. One reason for this is that Huntington’s chorea patients may present with a psychotic illness that is indistinguishable from schizophrenia, paranoid psychosis, or manic depressive psychosis. The diagnosis of Huntington’s chorea cannot therefore be made until neurological signs develop, sometimes after considerable delay.\(^10\) From time to time geneticists studying the family of a Huntington’s chorea patient make the diagnosis retrospectively in a dead parent from perusal of the hospital notes. Presumably, among such undiagnosed patients there were some who possessed a new mutation and in whom the absence of a family history made the diagnosis more difficult.

In conclusion, I believe that it is incorrect to say that new mutations for Huntington’s chorea occur in...
less than 0.1% of sufferers. I believe the evidence shows that the true figure is nearer 10%. I therefore consider that the absence of a known affected relative should not deter a neurologist from diagnosing Huntington's chorea in a patient who shows the characteristic clinical features of the disease.

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References

Charcot-Marie-Tooth disease

SIR,

We read the paper by Brooks and Emery with great interest. We agree with the authors that in Charcot-Marie-Tooth disease slightly affected females are easily missed on clinical examination. If the mode of inheritance in a family is in question it is necessary to detect these female carriers.

The importance of examining nerve conduction in unaffected persons was stressed by de Weerdt and Fryns and van den Bergh. who studied families with the hypertrophic (or demyelinating) type of the disease. In these two families X linked inheritance seemed probable.

However, if the neuronal type of the disease is in question, motor nerve conduction studies are of no help, because motor conduction velocity is usually normal, especially in persons who are only slightly affected. Sensory conduction studies probably discriminate better between affected and unaffected persons.

We would like to draw attention to the use of late response studies (Hoffmann (H) reflex and F response) in hereditary polyneuropathies. In patients with chronic renal failure these studies were abnormal at a time when no clinical evidence of peripheral neuropathy existed and conventional motor and sensory nerve conduction studies were normal. Recently we examined a family with the neuronal type of Charcot-Marie-Tooth disease in which X linked heredity seemed likely. H reflex investigation appeared to discriminate well between affected and unaffected subjects.

In future studies, investigation of the H reflex in families with Charcot-Marie-Tooth disease may contribute to detection of carriers with only minor symptoms and possibly to more insight into the pathophysiological backgrounds of the different genetic forms of Charcot-Marie-Tooth disease.

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References

This letter was shown to Dr Brooks and Professor Emery, who reply as follows:

SIR,

We agree with Drs Heimans and Lindhout that full electrophysiologic investigation is necessary in the assessment of patients with Charcot-Marie-Tooth neuropathy and their families.