Mutation in Huntington's chorea

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Huntington's chorea is inherited as an autosomal dominant and in the majority of published pedigrees the disease appears regularly in every generation. If the information is available, the disease can sometimes be traced through many generations over a considerable span of time. Investigation of the original family group described by Huntington has made it possible to trace their origin to the village of Bures in Essex whence they migrated to America in 1630 (Vessie, 1932). It is exceptional to be able to follow the disease back so far and this is usually because too little is known about the earlier generations. Only occasionally is it possible to trace the origin of the disease to a mutation and few pedigrees illustrating this have been published.

For a mutation to be acceptable in this disease the following four criteria must be fulfilled:

1. The disease being investigated must have the three cardinal features of Huntington's chorea—namely, progressive chorea and dementia, together with autosomal dominant inheritance. The latter feature is worth emphasizing, since it is important that the disease produced by the mutation be shown to occur in more than one generation.

2. Both parents of the first case must have lived to such an age than it can be reasonably assumed that the disease would have appeared had they carried the abnormal gene. It is rare in this disease for symptoms to appear after the age of 70 and Bell (1934) reported only one case with onset over this age out of 460 cases. It must be almost unknown for symptoms to appear after the age of 80. Therefore the latter age can be taken as a convenient dividing line, although other authors have chosen an age of onset as low as 65 years (Reed and Neel, 1959).

3. Sufficiently reliable information about the health of the parents of the first case must be obtained to ensure that they were free of the disease. Ideally, the parents should be examined, but this is rarely practicable because they are often dead when it becomes clear that the disease is developing in the second generation—that is, their grandchildren.

4. The apparent mutant must be the offspring of both his alleged parents and not the illegitimate issue of an unknown parent who carried the abnormal gene.

A family is described in this paper which appears to show a mutation to the gene for Huntington's chorea. The first three criteria are fulfilled and this probably also applies to the fourth, bearing in mind that it is almost impossible to investigate legitimacy when all the parties concerned are dead.

THE AFFECTED FAMILY

The pedigree of the family is shown in Figure 1. There are five examples of Huntington's chorea, occurring in three generations.

CASE III 3 This woman was born in 1871 and died in 1944, aged 73. She developed severe chorea when aged 57, although for about 20 years she had been clumsy and tended to drop things. In later years she was clearly demented, but it has been difficult to discover when this started. She spent the last seven years of her life in a mental hospital. It is not known if a necropsy was performed.

CASE IV 2 This man, the son of Case III 3, was born in 1893, and died in 1961, aged 68. His chorea became severe at the age of 51, although it had been present in a mild form since his late 30s. During the last year or so of his life he was moderately demented. He was admitted to a mental hospital only two weeks before his death and again it is not known whether a necropsy was performed.

CASE IV 3 This woman was the daughter of Case III 3. She was born in 1895 and died in 1960 aged 65. She developed chorea at the age of 50 and became demented a few years later. Both the chorea and the dementia were progressive and she died during her third stay in a mental hospital. A necropsy was not done.

CASE IV 5 This man was the propositus. He was born in 1900 and was aged 68. Apart from vertigo at the age of 49, he has always been in good health. At the age of 59 he developed mild chorea which has worsened gradually in recent years. He is now severely handicapped by choreic movements in the limbs and face, although at times he also shows torsion-like movements in the legs which are accentuated when he walks. He is only mildly demented in that his memory is fairly good, but his ability to do mental arithmetic is impaired. He can hold a normal conversation but his speech is slow, due, in part at least, to his chorea. No other abnormalities were found on examination and in particular his fundi were normal.

FIG. 1 The family tree.

CASE V 1 This woman, the daughter of Case IV 2, was born in 1923 and is still alive, aged 45. She developed chorea at 38 years of age and the dementia began when she was aged 40. Both the chorea and dementia have progressed, so that she is now a bed-ridden inmate of a mental hospital. She is barely able to hold a simple conversation and her memory and intellectual abilities are severely impaired. She shows mild chorea but extrapyramidal rigidity is also present. The latter was not present when she was first seen and may be due to thiopropazate (Dartalan), which she has been taking for several years. It is not suggested that she has the rigid form of this disease. Bilateral optic atrophy was the only other abnormal finding.

These five patients are the only known sufferers from the disease in this family and the remaining members of generations V and VI are free of the disease at the present time. Case III 3 had five children and of these IV 1 was illegitimate and nothing is known of her whereabouts or present health. The fifth child, IV 4, has been seen and appears healthy, showing no sign either of chorea or dementia. She is familiar with the features of the disease and has emphasized the startling similarity between the present appearance of her brother,

IV 5, and the appearance of his mother and siblings when they had the disease.

Information about generations I, II, and III has been obtained for the most part from Case III 8, who is the only surviving member of the sibship which contains Case III 3. She was familiar with the appearance of chorea, having often observed it in her sister, and she is certain that none of her other siblings were affected. Brief details of their ages and causes of death are as follows:

III 4 Born 1873. Died 1961, aged 88. Cause of death: 'old age'.

III 5 Born 1875. Died 1937, aged 62. Cause of death: not known.

III 6 Born 1877. Died 1954, aged 77. Died in a mental hospital from 'neurasthenia'. From his sister's description he may well have been demented but she is quite certain that he did not have chorea. Unfortunately, it has not been possible to obtain his medical records or to trace his descendants.

III 7 Born in 1878. Died 1943, aged 65, from complications following a hernia operation.

III 8 Born 1880. Still alive. Not demented. No chorea.

III 9 Born 1880. Died at birth. Twin brother of III 8.

III 10 Born 1883. Died 1904, in childbirth at the age of 21 years.

The parents of the first case (III 3) were both nursed in their final illnesses by their daughter (III 8) and she is quite certain that neither of them was significantly demented and that they did not have chorea.

II 1 Born 1848. Died 1934, aged 86. He was a thatcher and was always in good health. His death was attributed to 'old age'.

II 2 Born 1847. Died 1933, aged 86. She also had good health and is said to have died of 'old age'.

Some information is available on the grandparents of III 3, and again it is said that they did not have chorea.

I 1 Details of dates of birth and death are not known. He was a preacher, but little else is remembered about him except that at no time was it suggested that he had chorea.

I 2 Born about 1820. Died 1883 of heart failure.

I 3 Born 1819. Died 1895, aged 76. In his latter years he was nursed by his grand-daughter (III 8) who maintains that he did not have chorea.

I 4 Born 1826. Died 1888, aged 62. Death was due to drowning after falling into a dyke.

COMMENT

From the information obtained it appears that generation II was definitely free of chorea and that generation I was very probably free of it as well. The first case is III 3 and from her the disease descends as an autosomal dominant. The disease is apparently stereotyped in the family and consists of chorea and dementia with onset in the sixth decade, although V 1 is an exception to this in that her symptoms started at the age of 38. The age of death is fairly late, being 73, 68, and 65 years in the three choreics who have died. One living choreic is now 68 years old. Bell (1934) gave the average age of onset of symptoms as 35.5 years and the average age of death as 53.6 years in men and 52.6 years in women. Insufficient information is available to enable an opinion to be passed as to whether anticipation—that is, the appearance of symptoms at an earlier age in each generation—has occurred or not.

Case V 1 has one unusual feature in that she has optic atrophy. Neither its duration nor cause is known. Her uncle IV 5 has normal optic discs.

It is also of interest that III 6, the brother of the original case, had a dementing illness in his latter years. It has been noted previously (Bell, 1934) that mental disorders are fairly common in the families of patients with Huntington's chorea.

DISCUSSION

The rate of mutation to the gene for Huntington's chorea has generally been regarded as low, in view of the rarity of unaffected parents who have survived beyond the usual age at which the disease manifests

itself (Pratt, 1967). As a part of a comprehensive study of the disease in the State of Michigan (Reed and Chandler, 1958; Reed and Neel, 1959; Chandler, Reed, and De Jong, 1960) an attempt was made to calculate a mutation rate. Reed and Neel studied a total of 231 choreics, 206 of whom had a parent with chorea, seven had parents free of chorea, and insufficient information was available on the parents of the remaining 18. From this data and from the calculated frequency of heterozygotes in Michigan (1.01×10^{-4}) they calculated a mutation rate of 5.4×10^{-6} mutations/locus. They emphasized that this rate was probably too high, even though it was one of the lowest ever proposed for any hereditary disease.

In her review of the literature on Huntington's chorea, Bell (1934) described 151 pedigrees, but in only five of these is there evidence of a mutation as judged by the criteria referred to earlier. In each of these five pedigrees (numbered 3, 40, 57, 66, and 106) the disease appears in two or more generations, the inheritance is characteristically autosomal dominant, and the unaffected parents of the apparent mutant died in their 70s or 80s, except in pedigree 40 in which they are described as having lived to be 'old'. Pleydell (1954) described another example of a probable mutation in which the parents of the mutant lived to be 70 and 71 years old respectively. There are also other recorded instances of possible mutations, notably in the communications by Minski and Guttman (1938) and by Lyon (1962a); however, in each there is not sufficient information about the earlier generations to make it certain that they were free of the disease. A few pedigrees have been published containing several examples of the disease in the same generation without involvement of the second generation (Bell, 1934 (pedigree 57); Reid, 1960).

It is evident, therefore, especially from the work of Reed and Neel (1959), that mutation does occur occasionally in Huntington's chorea. Furthermore, the examples quoted above and the pedigree described in this paper would appear to exemplify this phenomenon. However, certain difficulties arise in the recognition of a mutation and these can influence the assessment of the true mutation rate. For example, Lyon (1962b) described a condition which he termed 'non-hereditary chronic adult chorea' in two subjects suffering from illnesses apparently indistinguishable from Huntington's chorea but in whom the parents, offspring, and other relatives were entirely free of the disease. If this is to be accepted as a separate clinical entity, then there is a risk that it may be confused with Huntington's chorea. A diagnostic error of this kind would, of course, make the apparent mutation rate higher than it would be otherwise. Chandler *et al.* (1960) in the

Michigan survey studied 801 choreics and found 36 without a family history and they regarded these 36 as being mutants. It is possible, however, that some of these patients had non-hereditary adult chorea. This difficulty was appreciated by Heathfield (1967).

The possibility of non-penetrance is a further theoretical obstacle against the correct recognition of a mutation. Indeed, this point was made by Reed and Neel (1959) who stated that in their study of 196 kindred containing the disease 'no specific instances of mutation in Huntington's chorea could be demonstrated because non-penetrance could not be definitely excluded.' In this context the latter means that an individual supposedly carrying the abnormal gene has survived well beyond the accepted upper age limit for the onset of the disease. Recognition of a carrier is contingent upon the fact that one of the individual's parents and some of his children suffer from the disease. Non-penetrance can appear to occur, of course, if the carrier dies before the expected age of onset of the disease, a phenomenon well illustrated in a pedigree recorded by Spillane and Phillips (1937) in which the disease was shown to be transmitted through two generations by carriers who died young. It would appear that true non-penetrance is a very unusual occurrence, since it has been possible to discover only one recorded example in the literature. This is to be found in pedigree 44 described by Bell (1934) in which is included a 78-year-old man who was free of the disease himself, although both his father and son were affected. If non-penetrance were, in fact, common, then it is probable that more examples would have been recorded. Clearly, more information about its frequency is required before its role as an alternative explanation to mutation can be assessed.

Reed and Neel (1959) have emphasized a further possible difficulty in the recognition of a mutation. They illustrate this in their description of a family in which there appeared to be only one example of the disease. However, it was later found that one of the parents was, in fact, suffering from chorea in mild form and that it had passed unnoticed by other members of the family. In this way the error of supposing that a mutation had occurred was avoided. The possibility of such an error was constantly kept in mind in investigating the present family and it would appear virtually certain that the parents in generation II were quite free of the disease.

Heathfield (1967) has referred to yet another

difficulty. In his survey of the prevalence of Huntington's chorea in the North East Metropolitan Region he found there were occasional examples of reluctance to admit the existence of the disease in a family. He considered that this was because of a desire to avoid the stigma of being a member of a 'tainted' family. This problem does not, however, arise in the family described in this communication.

In conclusion, it would appear that in the pedigree we have described a mutation to the gene for Huntington's chorea occurred in generation III. Thereafter the disease has descended through two further generations, and there is good reason to believe that there was no evidence of its existence in at least two antecedent generations.

SUMMARY

A family is described in which a mutation to the gene for Huntington's chorea is believed to have occurred. The criteria for acceptance of such a belief are outlined and the possible errors in interpretation of the evidence are discussed.

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