LETTERS TO THE EDITOR

Huntington’s disease in two unrelated Arab kindreds and in an Afghani family resident in Saudi Arabia

Huntington’s disease (HD) has its highest prevalence rates in European populations and in certain other ethnic communities around the world, in which the HD gene was probably introduced by Europeans.1 We report here classical HD in two unrelated Arab kindreds and in an Afghani family, all resident in Saudi Arabia. In all three kindreds, an original European source of the disease gene was possible, although this could not be documented.

FAMILY 1
All members of family 1 were Saudi Arabian Arabs living in Jedda and Makkah (Mecca). The pedigree (figure) indicates mendelian autosomal dominant inheritance. There were no known foreign antecedents.

III-3, the proband, was a 55 year old woman with a 10 year history of grimacing, choreoathetosis, dysarthria, ataxia, and progressive mental deterioration. She was now emaciated, almost mute, and unable to walk without assistance. Dementia with incontinence was present, but she was cooperative and still obeyed simple commands. There was no evidence of pyramidal tract or cerebellar dysfunction. Routine laboratory investigations, including basic haematological and liver function tests, showed no significant abnormality. Magnetic resonance imaging (MRI) of the brain indicated advanced atrophy of the caudate nucleus and putamina, and generalised cortical atrophy with dilatation of the ventricles. The distance between the caudate nuclei was 32 mm (normal range 12.5–15 mm), indicating severe atrophy of the nuclei.1

III-5, a 52 year old man, had early HD with grimacing, sparse choreoathetoid movements, dysarthria, and ataxia. He also had personality change and intellectual deterioration. III-6 had the same symptoms in middle age, but later died of pulmonary tuberculosis. III-8, a 40 year old woman, developed early features of HD when about 35 years old. She had generalised choreoathetosis, advanced dementia, and was bedridden. No investigation had been carried out. IV-3, a 35 year old man, was suspected to have early HD. He had recently developed personality change and severe lapses of memory with some nominal dysphasia. Significantly, his 10 year old son was reported to have developed signs of mental impairment associated with generalised seizures about three years earlier, but detailed information was not available. Family members initially requested DNA studies and predictive tests, but later changed their minds. Subsequently, they refused to attend follow up appointments.

FAMILY 2
All members of the second kindred were Saudi Arabian Arabs living in Riyadh. There were no known foreign ancestors. The family pedigree supported autosomal dominant inheritance, with three successive affected generations.

The proband, a 48 year old woman, presented with psychiatric symptoms during her last pregnancy when she was 37 years of age. She made a suicidal gesture by swallowing tablets, and later became paranoid with delusions of persecution. In due course she developed grimacing and choreoathetoid movements in her lower limbs. When assessed, she had marked dementia, dysarthria, generalised choreoathetosis, and ataxia. Routine haematological and biochemical tests were normal. MRI of the brain showed dilatation of the subarachnoid spaces including the cortical sulci, Sylvian fissures, and basal cisterns, and slight enlargement of the ventricles suggesting early cortical atrophy. The distance between the caudate nuclei was 22 mm, indicating marked atrophy of the nuclei.1 The patient’s family rejected the diagnosis, refused further investigation, and did not attend for follow up management. Subsequently, they sought second opinions at other centres in Saudi Arabia and overseas, but they still did not accept the diagnosis.

The patient’s mother, who died (age unrecorded) in a hospital, was reported to have had HD. The patient’s maternal aunt was diagnosed to have HD at the age of 50 years. A CT scan of the brain was reported to be “consistent with Huntington’s chorea”. No other family member was reported to have been affected by HD.

FAMILY 3
This family from Afghanistan had been resident in Makkah for many years. The family pedigree indicated mendelian autosomal dominant inheritance with three affected generations. The proband was a 41 year old man who first developed symptoms of HD when in his late teens with anxiety and excessive fidgeting. When he was about 23 years old, he developed choreoathetosis, and, later, dysarthria, ataxia, and progressive dementia. His younger brother died of HD at 42 years, and another sister was also choreic. The patient’s maternal grandmother, also born in Afghanistan, was reliably reported to have developed the typical features of HD in middle life, and died after some years, but further details were not available. The family has not yet been approached regarding the possibility of DNA studies.

Comment
The diagnosis of HD in the three unrelated families was based on the typical features of chronic choreoathetosis and dementia, beginning in early to mid-adult life, with evidence of autosomal dominant inheritance. The mean age of onset of clinical disease in patients in the first two families was approximately 39 years. There was no evidence to suggest that other conditions, for example, ataxia, chorea, and the atrophy of basal nuclei and putamina, were not caused by the hidden HD gene. The MRI of the brain is superior in this regard, identifying early evidence of atrophy of the caudate nucleus, putamina, and the cortex. The distance between the caudate nuclei is most reliable indicator of the diagnosis of HD, with a range in choric subjects of 15.5–32 mm (normal range 12.5–15 mm). It was notable that the 10 year old son of IV-3 had a three year history of mental impairment and generalised seizures. These signs may occur in juvenile HD and, further, juvenile cases are more likely to have an affected father. Further investigation of this child is planned.

It would be interesting to undertake DNA studies to ascertain if the HD gene in choric subjects had the same range of CAG nucleotide triplet repetitions (37–86) observed in all other HD patients. As noted, our families 1 and 2 have so far rejected DNA studies (and predictive testing), but hopefully they will eventually change their minds since so many of them are at risk for HD.

Unusually, genetic counselling has not been well accepted by our families. They did not fully accept the scientific explanation of HD and the advice that persons at risk should avoid having children until their status had been established. A contributing factor to this was their very strong religious faith, and

![Pedigree of family 1 indicating autosomal dominant inheritance.](http://jmg.bmj.com/10.1136/jmg.31.10.819)
everyone involved in counselling them has to be sensitive to their beliefs and adherence to Islam.

To our knowledge, HD has not been previously recorded in Saudi Arabia, nor in Afghanistan. Although European ancestry was not reported in any family, the disease gene could well have been introduced to them in the last century by foreigners visiting Red Sea or Arabian Gulf ports and, in the case of Afghanistan, travelling along traditional trade routes. Studies have shown that even the most isolated population affected by HD might have had European visitors in previous centuries. At present, the prevalence of HD in this population cannot be estimated, but it is likely to be comparatively low.

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The Prader-Willi-like phenotype in fragile X patients: a designation facilitating clinical (and molecular) differential diagnosis

We thank Gillessen-Kaesbach and Horsthemke1 for their comment on our paper “Clinical and molecular studies in fragile (X) patients with a Prader-Willi-like phenotype” in the March 1994 issue. The use of “like” syndromic designations generally invites discussion. We nevertheless chose to describe this rare phenotype of the fragile (X) syndrome in direct comparison with the Prader-Willi syndrome (PWS). The eight fragile (X) patients described in our paper showed a special subphenotype consisting of mental retardation, a full, round face, truncal obesity, hypogonadism, small, broad hands and feet (all prominent PWS symptoms) and regional skin hyperpigmentation. Moreover, they lacked major features of the Martin-Bell phenotype described in the majority of fragile (X) patients: a long face with large everted ears and megalotestes. Therefore the suggestion by Gillessen-Kaesbach and Horsthemke that these eight patients are just obese fragile (X) patients would be an insufficient clinical description of this special sub-phenotype. Considering the erroneous clinical diagnosis of PWS in two patients, the (partial) resemblance to classical PWS, and the necessity for a recognisable name for this special subphenotype we suggested the name “Prader-Willi-like”. We hope that this will make clinicians aware of the need for performing DNA analysis for both chromosome 15q abnormalities and the FMR-1 gene mutations in the mentally retarded patients presenting with either the Prader-Willi syndrome or the Prader-Willi-like subphenotype of the fragile (X) syndrome.

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Arthrogryposis multiplex congenita, renal dysfunction, and cholestasis syndrome

We read with interest the article by Horslen et al1 “Liver histology in the arthrogryposis multiplex congenita, renal dysfunction, and cholestasis (ARC) syndrome: report of three new cases and review”. We hope to comment on the possibility of variation of histological findings in the liver within a single syndrome of arthrogryposis multiplex congenita, cholestatic liver disease, and renal impairment, or the existence of two separate conditions.

Whenever paucity of intrahepatic bile ducts was seen on hepatic histology, patients died between the ages of 3 months 2 weeks and 7 months.1,2 However, when lipofuscin deposition was present without paucity of intrahepatic bile ducts, patients always died before they were 3 months 2 weeks old.3,4 As it is unlikely that paucity of intrahepatic bile ducts could resolve, and as lipofuscin deposition only, whenever present, was always seen at the time of death, the possibility that the two histological features are different stages in the evolution of the disease can be discarded. However, the different hepatic histologies may be two non-specific changes resulting from the same insult, as was suggested by the presence of features compatible with both groups in one patient.4

We propose that the lipofuscin deposition occurs only when the liver is more severely affected and this would imply a worse prognosis. As there are two sibships where the first patients died when they were more than 4 months old and the younger affected brothers when they were younger than 3 months old, we would suggest that the former had paucity of intrahepatic bile ducts and the latter had lipofuscin deposition. Unfortunately, in only one of the four patients were hepatic histological features studied2 but the result agrees with our hypothesis.

If the different clinical outcomes in the same sibship result from different hepatic histology, this would support the suggestion that different histological findings are not more than variation within a single syndrome. However, this remains an open question until the two are reported in the same sibship.

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