Conference report

World Federation of Neurology (WFN) Research Group on Huntington's Disease, Vancouver, 29 June to 2 July 1989

The 13th International Workshop of the WFN Research Group on Huntington's disease, organised by Dr David Stevens (Secretary General) and hosted by Dr Michael Hayden, was attended by 70 participants from 17 countries. The number of participants and the amount of new research data presented have steadily increased since the first workshop (also held in Canada) in 1967.

A key session was held on mapping the Huntington's disease (HD) gene. Since the original localisation of HD to chromosome 4p16.3, there has been considerable impetus to obtain and order more closely linked markers. Data on new probes D5 (*D4S90*) and 2R3 (*D4S141*), both of which are telomeric to G8 (*D4S10*), were presented and radiation mapping allowed the independent ordering of these markers relative to one another. Intensive efforts to clone the telomere has led to recent success using a yeast artificial chromosome (YAC) vector and so a distal limit has been set to the localisation of the HD gene. Three centres (Cardiff, Vancouver, and Rome) have detected strong linkage disequilibrium between HD and various DNA markers. In a study of linkage between G8 (*D4S10*) and HD in 63 affected families from around the world, there was no evidence of multilocus heterogeneity.

Preliminary reports of predictive testing from several centres (Vancouver, Boston, Baltimore, Cardiff, Manchester, Leuven, Leiden, and Adelaide) were presented. Altogether about 160 subjects at risk have had presymptomatic tests. Short term follow up of those who have had an increased risk on presymptomatic testing does not indicate significant psychiatric morbidity. A lively debate highlighted the many unresolved problems in this area. The Committee appointed by the WFN and the International Huntington's Association (IHA) has revised the guidelines (*J Med Genet* 1990;27:34-8) on predictive testing which were originally formulated in 1985. At a joint session of the WFN and the IHA, several subjects who had been given a presymptomatic test result (favourable, adverse, and uninformative) spoke movingly of their personal feelings and the

impact of the test result; the need for careful counselling was underlined.

There were other sessions on epidemiology, clinical aspects, imaging, pathogenesis, experimental therapeutics, and general genetics.

Regarding epidemiology, it was reported that there are no cases of HD in the indigenous Maori or Aborigine populations and similarly there are no known cases of Eskimo origin. Finland and Japan are countries of low prevalence. Recently, a HD family has been located in Peru and one North American Indian family was reported at the meeting. In Cuba, as in Venezuela, HD is of Spanish origin.

In the clinical session, unusual phenotypes were presented, including a video of a patient with myoclonus. The first series of HD patients suffering from delusional infestation (Ekbohm's syndrome), a rare form of psychosis, was reported. Alcohol misuse did not appear to be common among HD sufferers. Differential diagnosis of HD should include conditions like familial Pick's disease, acanthocytosis, and dentatorubropallidolulysian atrophy.

In vivo brain metabolism studies, such as positron emission tomography (PET) using fluorodeoxyglucose (FDG), have produced conflicting results about resting brain activity in HD patients. The Los Angeles/Vancouver groups reported decreased caudate metabolism, while the Michigan investigators did not. Such studies have also been performed in the at risk subjects and it was suggested that abnormal striatal glucose utilisation precedes the onset of symptoms.

In the pathogenesis session, it was reported that striatal abnormalities in the brain are hallmarks of HD although one centre recently published a series of five cases of HD without striatal changes on neuropathology. Several other conditions, such as Pick's disease, Alzheimer's disease, and status marmoratus, can cause striatal pathology.

The excitotoxin hypothesis remains useful in trying to understand the basis of chorea. It was suggested there was an abnormality in NMDA (N-methyl-D-aspartate) mediated processes and it is known that

NMDA receptors are depleted in HD. Further studies involving NMDA receptor agonists (quinolinic acid, L-glutamic acid, D-AP5) and antagonists, such as the new non-competitive antagonist, MK-801 (also a potent anticonvulsant on kindled seizures), should help clarify neuroreceptor abnormalities.

The session on experimental therapeutics unfortunately showed that successful and specific pharmacological intervention in HD is still remote. A large, double blind, placebo controlled trial of baclofen in patients with early HD failed to show superiority of the active drug. However, useful data on the natural history of HD, such as the rate of functional decline, were obtained from this investigation.

The general genetics session covered many different areas. The largest known pedigree of any genetic disorder, not just of HD, is from Venezuela. This pedigree contains about 7000 members with over 100

living affected subjects. In a study of homozygotes in this pedigree, it emerges that there are no phenotypic differences (monitored by regular neurological and psychological examinations) between heterozygotes and homozygotes in HD. The criteria for mutation in HD are stringent, yet cases of possible mutation from Norway and Boston were presented. Data on the age of onset and sex transmission of HD from the Wales register of 892 persons (both living and dead) were discussed. There is an excess of paternal transmission (4:1) in juvenile onset cases (that is, onset before the age of 20 years) but, unlike an earlier Boston study, there is no evidence of an excess of maternal transmission in late onset cases (that is, onset after the age of 50 years).

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