Conference report

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A workshop on facioscapulohumeral (Landouzy-Déjérine) disease, Manchester, 16 to 17 November 1988

Facioscapulohumeral disease (FSHD) is an autosomal dominant condition with wide variation in age of onset and severity. Typically, onset is in childhood with facial weakness, but first clinical presentation is usually in the teens or early adulthood with symptoms of shoulder girdle weakness. Progression may be slow, but weakness often extends to involve ankle dorsiflexors and proximal lower limb muscles in addition to more extensive upper limb weakness. Successful mapping of the FSHD gene would facilitate the provision of accurate genetic counselling to subjects at risk, help resolve questions of genetic heterogeneity, enable prenatal diagnosis, and, in characterisation of the genetic defect, promote future research into rational therapies.

With funding from the Muscular Dystrophy Group of Great Britain this workshop was convened in order to pool linkage data for delineation of a current exclusion map; to organise future collaboration which will reduce unnecessary duplication; and to discuss the questions of genetic heterogeneity, age dependent penetrance, and presymptomatic detection, answers to which are required for interpretation of linkage data. The 20 participants included four groups who contributed linkage data: Padberg/Frants (Leiden), Upadhyaya/Sarfaraizi/Lunt/Noades (Cardiff, Manchester, and London), Lucotte (Paris), and Pericak-Vance/Siddique/Shaw (Durham, NC and Manchester).

Clinical aspects

Although the names of Landouzy and Déjérine are used eponymously in FSHD, earlier descriptions by Hone (1842) and Duchenne (1868) were discussed (Gardner-Medwin, Newcastle). The first description, however, was perhaps the Sphinx of Greek mythology. In a comprehensive clinical summary from study of 15 large families from Holland, Padberg emphasised that facial weakness, although usual, is not obligatory, but is required in at least one family member for ratification of a diagnosis of FSHD. Although 'abortive' cases

(affected family members unaware of symptoms) may account for 20 to 40% of all cases, the frequency of disabling lower limb involvement is as high as 10 to 20% by middle age (Padberg, Lunt: Manchester). These figures promoted discussion on whether the term 'facioscapulohumeral' is the most appropriate, as it had often misled both patients and doctors. To minimise clinical prejudice, the workshop recommended use of the term 'Landouzy-Déjérine disease', already used widely in Europe, and honouring the authors who first recognised the condition as a distinct entity.

Resolution of the question of genetic heterogeneity is required to validate the summation of lod scores from different families. Padberg, Lunt, and Siddique (Durham, NC) had each found no evidence to support genetic heterogeneity for clinical presentation, as each reported as much variation within large families as between them in distribution and severity of weakness, including cases with early peroneal involvement. Clinical discussion concentrated on whether dominantly inherited Landouzy-Déjérine disease is a single genetic entity, or whether a facioscapulohumeral syndrome can occur with a type of spinal muscular atrophy, with a type of mitochondrial myopathy, and with a type of muscular dystrophy. In the one large family with a facioscapulohumeral syndrome diagnosed as mitochondrial myopathy, pelvic girdle onset and lingual and cerebellar involvement indicate a distinct, but recognisable, genetic entity. Cumming (Manchester) presented results of 62 quadriceps biopsies, reviewed blindly, from patients with a facioscapulohumeral syndrome; seven (11%) showed 'dystrophic' changes and 45 (73%) suggested a neurogenic aetiology. Analysis of familial correlation is awaited. Similar biopsy features of small angular fibres, regeneration, and fibre size variation, were noted by Padberg, but in none was spinal muscular atrophy diagnosed. Three families were known (Lunt) in which diagnoses of spinal muscular atrophy and muscular dystrophy had been made independently in different members, causing

duplication of linkage results in one. The workshop was reminded of the confirmation from cDNA probes of a diagnosis of Becker muscular dystrophy in patients previously diagnosed from interpretation of biopsies as having X linked spinal muscular atrophy. In proposing that Landouzy-Déjérine disease is likely to be a single genetic entity, it was suggested (Emery, Edinburgh) that it may be a disease of the whole motor unit, rather than having a strictly neurogenic or myogenic aetiology.

Asymmetry, often interpreted as a sign of myelopathy, had been noted in the majority of cases by all participants. The right arm is usually the weaker and a causal relationship to handedness was suspected. Disuse or overuse of a limb can precipitate deterioration, and the workshop agreed that swimming or other gentle exercise was beneficial. The results of scapular fixation in cases with severe weakness were discussed favourably (Padberg).

Gardner-Medwin presented a personal series of cases with congenital or infantile presentation, which from published reports may be associated with hearing loss or with Coates-like retinal lesions or both. In most, a dominant family history of FSHD could be elicited, and in isolated cases there was no parental consanguinity. In one case with a probable dominantly inherited deafness, cosegregation with FSHD could not be proven. None had a known retinal lesion. Fitzsimons (Sydney) discussed the finding of peripheral retinal capillary abnormalities in 56 out of 75 (75%) patients from several different families with FSHD. Since other investigators have failed to confirm significant retinal abnormalities in more than 1/10 patients, and while allowing for technical difficulties, concern was expressed over the possibility of false positive retinal or neurological diagnoses. The association of FSHD, particularly of congenital onset, with retinal changes or hearing loss or both may represent genetic pleiotropy rather than heterogeneity, or result from contiguous gene deletion. Further studies are indicated.

Accurate genetic counselling in FSHD requires reliable data for age dependent penetrance and for the likely severity of heterozygotes (discussed above). From data on 12 families, with ascertainment bias minimised in the analysis, figures were presented (Lunt) for penetrances of 0 to 40% for ages 0 to 9 years, 58% at 10 to 14, 86% at 15 to 19, and 95% at 20 years or over. Three obligate heterozygotes over the age of 40 years with normal clinical examination were discussed, as they belie an eventual penetrance of 100%. Extrapolation from retrospectively reported ages at onset suggested correlation with severity such that asymptomatic young adults have a reassuringly good prognosis.

The potential use of serum creatinine kinase (CK), computerised tomography (CT), and retinal angiography as presymptomatic tests was discussed. A raised CK with 'mild' disease occurs in only 37% of females and 75% of males and is unrelated to age (Lunt). Hence, both CK and retinal angiography were felt to be unreliable as predictive tests. Cumming presented results of CT scans, suggesting that changes in muscle, especially psoas, can be detected before onset of clinical weakness. CT scanning could prove to be a reliable method of presymptomatic detection in FSHD, especially if similar changes occur in facial muscles.

Gene mapping

Since exclusion of all unaffected subjects from linkage analysis would leave insufficient data, an upper age limit of 15 years was chosen for exclusion, above which it was agreed to use the presented figures of age dependent penetrance for age weighting segregation data from unaffected subjects. Standard clinical criteria for definition of affected status from interpretation of minimal clinical signs were also required. While empirical combinations of physical signs scored as 'hard' and 'soft' in those at risk might be helpful, the workshop felt that subjective clinical assessment by an experienced observer was sufficient, provided that any cases of clinical doubt were excluded from linkage analysis. Possible indication of presymptomatic affected status from serum CK, CT scan, biopsy, and retinal changes could be helpful. The workshop was unanimous in cautioning that false positive and false negative diagnoses based on the accounts of other family members are commonplace. Segregation analysis should be restricted to subjects examined personally. To allow for possible genetic heterogeneity, results for families diagnosed as 'spinal muscular atrophy' were to be noted separately from those diagnosed as 'muscular dystrophy'. However, the most efficient initial approach to exclusion mapping was accepted as being the combination of linkage results from all families with a dominantly inherited facioscapulohumeral syndrome.

Padberg (1984) added to earlier linkage studies in FSHD, excluding close linkage ($\theta=0.1$) at 13 loci for blood group and protein polymorphisms. Possible linkage to *Gm* (location 14q32.3) was discounted by recent further data presented at the workshop (Padberg, Lucotte, Noades: London). Combination of all linkage results presented at the workshop with those previously reported identified five chromosomal regions (4q, 5q, 11, 17q, 19q) where small positive lod scores (sexes combined) were obtained with, respectively: *MNS*; *D5S37*; *ETS1* & *HRAS1*;

D17S36 & NGFR; APOC2 & D19S9. No pooled lod score, or score from a single family reached 3.0, accepted as the minimum score required for recognition of linkage. The EXCLUDE program (Edwards) showed that a substantial proportion of the genome had been excluded as a probable location for FSHD (Sarfarazi, Cardiff). Regions lacking data included 1q, 2q, 3, 5p, 6q, 8p, 9p, 10, 12p, and 15. Future reports should give lod scores separately for male and female meioses. Maximum efficiency in the use of further DNA probes will be achieved by continued collaboration. The workshop agreed to relay all new linkage results to one centre (Sarfarazi, Cardiff) for compilation of an updated exclusion map for distribution to participants every three months.

As possible clues to gene location, reports were invited of cases of FSHD associated with chromosomal anomalies or other genetic conditions. Previous association with retardation, deafness, and Coates-like retinal changes was noted. One isolated child with features of FSHD, deafness, and retardation has a *de novo* deletion of 18q22.2-18qter (A C Berry, 1987, personal communication), but linkage studies do not support this as a location for FSHD (Upadhyaya, Cardiff). Karyotyping of all

other isolated cases with retardation or family history of recurrent miscarriages was proposed. In two families, possible association with familial adenomatous polyposis coli has been noted (L P Rowland, 1988, personal communication).

To avoid prejudice in anticipated future attempts at correlation of clinical features with any heterogeneity of linkage, it was proposed that certain clinical parameters in affected subjects from each family studied should be recorded prospectively. These include severity, age at onset, distribution of muscle weakness, facial involvement, asymmetry, current classification of aetiology as neurogenic or myogenic, serum CK, hearing loss, and retinal changes.

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P W LUNT
*Department of Medical Genetics,
St Mary's Hospital,
Whitworth Park,
Manchester M13 0JH.*