Report of ENMC workshop on the limb-girdle muscular dystrophies

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This workshop of 37 participants took place in Soest, The Netherlands, from 28 February to 1 March 1992. It was organised by Dr Kate Bushby, with assistance from her colleagues in Newcastle upon Tyne, and from Professor Alan Emery and others at the European Neuromuscular Centre (ENMC) and European Alliance of Muscular Dystrophy Associations (EAMDA). Financial support was provided by the ENMC, the Association Française Contre les Myopathies, and the Commission of the European Communities. Participants submitted clinical information on the cases they had seen of limb-girdle muscular dystrophy (LGMD) in advance of the workshop. The aims of the workshop were (1) to review the clinical experience of the participants of all forms of LGMD; (2) to establish clinical criteria to distinguish the different entities included within the compass of LGMD; and (3) to discuss the molecular genetic work in progress, and to coordinate the future work required to identify the relevant genes. The workshop was organised by topic into five sessions.

The first session was an introduction to 'the problem'. After a speech of welcome from Professor Emery, Gardner-Medwin (Newcastle upon Tyne) discussed the nature of the diagnosis of LGMD, likening it to the Hydra that was eventually slain by Herakles. Beckmann (Paris) then discussed the difficulties of performing linkage analyses with the clinical material available, there being few large pedigrees except in small inbred populations. The use of small families with affected sibs in linkage analysis assumes that the inheritance is recessive, rather than dominant with parental mosaicism or reduced penetrance.

Suthers (Oxford) presented information about dystrophin, about the dystrophin related proteins (DRPs), often known as dystrophin isoforms, derived from the same gene at Xp21 by transcription from different promoters and by differential splicing, and about the dystrophin-like protein (DLP), the autosomal homologue encoded at a locus on chromosome 6, sometimes termed the DMDL gene. Suthers suggested that his terminology was clearer than the use of DRP to refer to the chromosome 6 homologue. Because there may be more than one DLP, he used the term 'utrophin', because so ubiquitous, to refer to the DLP encoded on chromosome 6. This is conserved across species, and is found particularly in smooth muscle and at neuromuscular junctions. Linkage analysis with the available LGMD families, including some from North Africa and Brazil, has found no evidence to implicate this locus in the disease.

Finally, Bushby discussed the heterogeneity of LGMD, and presented an outline of the clinical data that had been submitted to her before the meeting of more than 90 families and sporadic cases of LGMD. She grouped families in terms of inheritance pattern, age of onset, rate of progression, and pattern of muscle involvement.

The second session reviewed data from cases of recessive LGMD in specific population groups. Fardeau (Paris) presented his study of families from Reunion Island: the onset is usually at 8 to 12 years, but can be delayed to 30 years, with proximal weakness of upper and lower limbs including scapular winging. Gluteus maximus, hip adductors, latissimus dorsi, and the scapular muscles are involved first; the rate of progression is variable, even within families, but usually spares the face and the small muscles of the hand. Shortening of the Achilles tendon is found. Hypertrophy is unusual. The serum CK is substantially raised, the ECG is normal, and the EMG is myopathic. Linkage to markers from the region of the fibrillin gene on chromosome 15 has been established by Beckmann, with a lod score of 5.5 for D1S25; the gene is localised to less than 10 Mb between 2 cM flanking markers.

Jackson presented data from his study of the LGMD found in the Amish people in Indiana. The clinical features are similar to those of the Reunion group, although calf hypertrophy is recognised more commonly, and linkage has also been found to the fibrillin gene on chromosome 15, with lod score > 9 at 4 cM.

Zatz and Passos-Bueno from Brazil described their pedigrees; 14 of 16 families had been excluded from linkage to utrophin on chromosome 6, six of 11 were excluded from chromosome 15, and two showed significant linkage to chromosome 15. The families linked to chromosome 15 showed intrafamilial variation in clinical course and calf hypertrophy; serum CK was increased 2 to 15 times. The other families had a preclinical 100 times increase in CK and variable calf hypertrophy (this did not help to distinguish the chromo-
some 15 families). Biopsy features also did not permit a distinction between the 15 linked and 15 excluded families.

In the third session, the recessive LGMD of DMD-like severity was discussed. Hamida presented the clinical findings of the Tunisian form of LGMD, which is at least as common as DMD in that population. Onset is usually at 5 to 9 years, and calf hypertrophy and hyperlordosis are common. Initial serum CK values are very high (up to 15,000) and then slowly decline. The families have shown no linkage to utrophin or to the candidate regions of chromosomes 15 or 5. Zatz described her experience of Brazilian families with DMD-like autosomal recessive disease: it is clinically indistinguishable from DMD, and serum CK values are similar. There is a tendency for some of the children to be confined to a wheelchair a bit later than in DMD, but with variation within a family. About 2-5% of males with apparent DMD have the recessive LGMD, a prediction from population data that has been confirmed by dystrophin analysis on muscle biopsies. Similar results were also reported by Grimm and Dubowith. Gardner-Medwin reported an incidence of 0.3 per 100,000, with one male child affected for every 100 births of males with Xp21 dystrophy. In the recessive LGMD, the pattern of muscle weakness is sometimes subtly different from that in DMD, but the tendency to early toe walking is not helpful in distinguishing them. An abnormal ECG is often useful in indicating the diagnosis of DMD.

Reports of less severe forms of recessive LGMD were presented in the fourth session: from Finland (one family had mild shoulder weakness only; another extended kindred had a proximal myopathy with onset in the second or third decades in some members, and a biallelic weakness with onset later in life in some other members), from Palestine (onset in infancy, or in late childhood through to early third decade), and from France and Britain (including a few families with early contractures of the upper limbs and sometimes spinal rigidity). Voit (Germany) reported studies of a recessive proximal LGMD with early onset of shoulder weakness, a rise in serum CK after the first few months, normal intelligence, and a variable cardiomyopathy. He described his immunocytochemical (ICC) findings on muscle biopsy from these cases, contrasted to DMD. The normal ribbed pattern of dystrophin seen on special preparations of fresh sarcolemmal membrane stripped from the rest of the fibre (with costomeres arranged orthogonally to the direction of the fibre, in relation to the alphaactinin Z lines) was found to lose its tight structured array, and this was apparent on standard dystrophin ICC as a broadening and fuzziness of the dystrophin fluorescence. The normal appearance of dystrophin was present in an adult case of LGMD. It was proposed that the molecular defect in the childhood LGMD is of a protein that links dystrophin to the cell membrane, perhaps one of the glycoproteins with which dystrophin is associated.

The fifth session was devoted to the dominant LGMDs. Speer presented linkage analysis of a large pedigree with late onset disease (mean age 28 years). A lod score of 10-8 at 12 cM was obtained with DSS21 and a set of microsatellite markers in that region around the fibrillin locus. Phenotype analysis showed onset at pelvic girdle before shoulder girdle, hyperlordosis, and some impairment of palatal function. Serum CK values were 10 times raised: this rise of CK rather than gradings of muscle strength was used in the linkage analysis. Marconi (Italy) reported a similar family, which showed some calf hypertrophy and hyperlordosis, and Bushby reported three families with weakness of hamstrings and scapular muscles. The hamstrings were weaker than quadriceps, asymmetry was apparent clinically, there were lobulated, flocular fibres on biopsy, and serum CK was only slightly raised. One family had 'terracing' of the shoulder muscles, as can be seen in facioscapulohumeral dystrophy. Jakobsen (Denmark) and De Visser (Netherlands) reported families with early onset but benign myopathies, including Bethlem myopathy.

The rest of the meeting was devoted to discussions of plans for future work, led by Gardner-Medwin and Suthers. These plans will be coordinated jointly by Dr Kate Bushby (Division of Human Genetics, 19/20 Claremont Place, Newcastle upon Tyne NE2 4AA, England) for the clinical studies, and by Professor JS Beckmann (Centre d'Etude du Poly morphisme Humain, Strangeways Research Laboratories, 27 Rue Juliette-Dodu, 75010 Paris, France) for the molecular studies. The clinical delineation of the genetically distinct forms of LGMD must be pursued. Given the limited range of clinical material available to most investigators, the coordination of research efforts in this way is clearly essential. The molecular work will focus on the genetically pure populations, and the development of analytic methods that will allow full information to be extracted from limited material.

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Bibliography


