5. Localio AR, Lawthers AG, Brennan TA, et al. Relationship between malpractice claims and adverse events due to negligence. N Engl J Med 1991;325:245–251.
6. Rolph JE, Kravitz RL, McGuigan K. Malpractice claims data as a quality improvement tool. Is targeting effective? JAMA 1991; 266:2093–2097.
7. Institute of Medicine. To err is human: building a safer health system. Washington, DC: National Academy Press, 2000.
8. Levinson W, Roter DL, Mullooly JP, Dull VT, Frankel RM. Physician–patient communication: the relationship with malpractice claims among primary care physicians and surgeons. JAMA 1997;277:553–559.

Editorial

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CME

Congenital muscular dystrophy

Searching for a definition after 98 years

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Finding a suitable classification for the muscular dystrophies is a formidable task. In the premolecular era attempts were based on phenotypic features that often erroneously separated entities (e.g., Duchenne and Becker dystrophies). In the molecular era new challenges arose with proven clinical heterogeneity from single gene defects (e.g., Miyoshi myopathy and limb-girdle muscular dystrophy[1]). The dilemma of classification is again brought into sharp focus in an article by Cormand et al. on congenital muscular dystrophy (CMD) in this issue of *Neurology*.[2]

For a century the nosology of CMD has challenged clinicians. The disease was first reported in 1903 by Batten, well-known for his description of juvenile neuronal ceroid lipofuscinosis.[3] For 50 years clinicians avoided the term CMD, using instead confounding designations such as "myatonia or amyotonia congenita." Thus, CMD was not even mentioned in the landmark classification of muscle disease set forth by Walton and Natrass in 1954.[4] The important publication of Banker et al. in 1957 rekindled interest in CMD especially in association with arthrogryposis multiplex congenita.[5] Nevertheless, as recently as 1986, Brooke crystallized the frustration experienced by many colleagues in a statement about the nosology of CMD: "just when I think I have the entities clearly in mind, a new patient comes along with features common to more than one of these entities. What is badly needed is some irrefutable biochemical test which will separate the diseases one from another."[6]

Brooke's wish was partially realized in 1994 through the observations of Tomé et al.[7] They reported that patients with "classical CMD" were deficient in merosin, the α2 chain of laminin-2, a major constituent of the basal lamina of skeletal muscle fibers linking the extracellular matrix to the dystrophin-associated proteins and integrins. The breakthrough by Tomé et al. permitted a subdivision into merosin-negative and merosin-positive CMD (table). The merosin-negative cases demonstrated clinical homogeneity (severe hypotonia, multiple contractures, delayed milestones, normal mentation) accompanied by variable degrees of central hypomyelination seen on neuroimaging. Further observations assigned CMD-negative cases to chromosome 6q22-q25 and mutations of the laminin α2-chain (*LAMA2*) gene were found.[8] A milder phenotype with partial deficiency of merosin was subsequently reported.[9]

The merosin-positive CMD (see the table) constitute a genetically more heterogeneous group. A gene locus (*RSMD1*) has been established on chromosome 1p35-p36 for CMD with rigid spine syndrome.[10] The disease presents in infancy with axial muscle weakness, early rigidity of the spine, nocturnal respiratory insufficiency, and prominent nasal voice. Ullrich disease is another merosin-positive CMD characterized by proximal contractures combined with distal joint laxity, delayed motor milestones (some learn to walk but the majority are wheelchair dependent), and normal intellegence.[11] Chromosomal linkage has not been established for this variant. A host of other merosin-positive CMD families have been described without known linkage. Some have normal intelligence and normal brain imaging referred to as "pure" CMD whereas others show varying degrees of mental retardation with abnormal brain imaging studies.[11]

A third grouping of CMD includes neuronal migration defects: Fukuyama CMD (FCMD), muscle–eye–

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Table *Classification of congenital muscular dystrophy (CMD)*

Disease	Chromosome	Gene
Merosin-negative CMD (complete or partial)	6q22–q25	*LAMA2*
Merosin-positive (MP)		
Rigid spine disease (RSMD1)	1p32–34	Unknown
Ullrich syndrome	Unknown	Unknown
Pure CMD	Unknown	Unknown
Other MP-CMD	Unknown	Unknown
Neuronal migration disorders		
Fukuyama CMD	9q31–q33	Fukutin
Muscle–eye–brain disease	1p32–p34	Unknown
Walker–Warburg syndrome	Unknown	Unknown
Other CMD with neuronal migration defects	Unknown	Unknown

brain (MEB) disease, and Walker–Warburg syndrome (WWS) (see the table). FCMD, an autosomal recessive disorder with mental retardation, epilepsy, visual impairment (myopia, congenital nystagmus, cortical blindness, optic atrophy, and choreoretinal degeneration) was described in 1960. The brain shows micropolygyria, pachygyria, and minor cerebellar alterations and the fukutin gene defect represents a novel mutation with a retrotransposal insertion of tandemly repeated sequences on chromosome 9q31-q33.[12] MEB, described in Finland by Santavuori et al. in 1977, shares features with FCMD but is milder with survival ranging from early childhood to the seventh decade.[13] Confusion between disorders of neuronal migration was heightened when WWS was described. Although similar to MEB, it is comparatively more severe, leading to death in the first few months of life.

The gene(s) causing WWS and MEB are not known but MEB has been localized to chromosome 1p32-p34.[14] For two decades similarities in MEB and WWS have added to the confusion of CMD nosology. In the current issue of *Neurology*, Cormand et al. report linkage and haplotype analysis that unequivocally demonstrates that WWS and MEB are distinct disorders.[2] Nineteen families, 16 consanguineous, of different ethnic origins from neuromuscular centers at sites in Europe, the Middle East, and the United States participated in these studies. All but one of the 11 MEB families demonstrated linkage to 1p32-p34 whereas linkage was excluded in seven of eight WWS families.

Thus, the extensive experience of Cormand et al. has delineated differences in CMD.[2] However, the turbulence expressed by Brooke in 1986 still exists because of unresolved dilemmas in the definition of the disease. Most fundamental is what permits a disease to be designated CMD. Certainly it is not the time of onset (infancy), the progression of disease, or even the joint contractures that delineate CMD. Other well-defined dystrophies may have onset in infancy (e.g., Duchenne), some irrefutable congenital myopathies are relentlessly progressive (X-linked myotubular myopathy, integrin $\alpha 7\beta 1$ deficiency), and joint contractures are a notable feature of Bethlem myopathy and Emery–Dreifuss muscular dystrophy (X-linked and autosomal dominant).

A challenge for the future must include a definition of CMD that sets it apart from other disorders. Alternatively, and perhaps more wisely, the time has come to drop the inaccurate, antiquated, and nondescript term CMD. How does it help us and why do we need it?

References

1. Liu J, Aoki M, Illa I, et al. Dysferlin, a novel skeletal muscle gene, is mutated in Miyoshi myopathy and limb girdle muscular dystrophy. Nat Genet 1998;20:31–36.
2. Cormand B, Pihko H, Bayés M, et al. Clinical and genetic distinction between Walker–Warburg syndrome and muscle–eye–brain disease. Neurology 2001;56:1059–1069.
3. Batten RE. Three cases of myopathy. Infantile type. Brain 1903;26:147–148.
4. Walton JN, Natrass FJ. On the classification, natural history and treatment of myopathies. Brain 1954;77:169–231.
5. Banker BQ, Victor M, Adams R. Arthrogryposis multiplex due to congenital muscular dystrophy. Brain 1957;80:319–334.
6. Brooke MH. A clinician's view of neuromuscular disorders. 2nd ed. Baltimore: Williams & Wilkins, 1986.
7. Tomé FM, Evangelista T, Leclerc A. Congenital muscular dystrophy with merosin deficiency. CR Acad Sci III. 1994;317:351–357.
8. Hebling-Leclerc A, Shang X, Topaloglu H, et al. Mutations in the laminin $\alpha 2$-chain gene (*LAMA2*) cause merosin-deficient congenital muscular dystrophy. Nat Genet 1995;216–218.
9. Nissinen M, Hebling-Leclerc A, Zhang X, et al. Substitution of a conserved cysteine-996 in a cysteine-rich motif of the laminin $\alpha 2$-chain in congenital muscular dystrophy with partial deficiency of the protein. Am J Hum Genet 1996;1177–1186.
10. Moghadaszadeh B, Deguerre L, Topaloglu H, et al. Identification of a new locus for a peculiar form of congenital muscular dystrophy with early rigidity of the spine on chromosome 1p35-36. Am J Hum Genet 1998;62:1439–1445.
11. Voit T. Congenital muscular dystrophies: 1997 update. Brain & Dev 1998;20:65–74.
12. Toda T, Segawa M, Nomura Y, et al. Localisation of a gene for Fukuyama type congenital muscular dystrophy to chromosome 9q31-33. Nat Genet 1993;5:283–286.
13. Santavuori P, Leisti J, Kruus S. Muscle, eye, and brain disease: a new syndrome. Neuropaediatrie 1977;8(suppl):553–558. Abstract.
14. Cormand B, Avela K, Pihko H, et al. Assignment of the muscle-eye-brain disease gene to 1p32-p34 by linkage analysis and homozygosity mapping. Am J Hum Genet 1999;64:126–135.