

A MODERN PERSPECTIVE ON SOME OF THE MOST HIGHLY CITED JNNP PAPERS OF ALL TIME

Unusual type of benign X linked muscular dystrophy

Alan E H Emery



Alan E H Emery from Green Templeton College, Oxford, describes the excitement of his trip as a single handed 'research laboratory on wheels' to the Appalachian Mountains to follow up a large family thought to have 'mild' Duchenne muscular dystrophy, which led him to delineate the disorder now known as Emery–Dreifuss muscular dystrophy

Duchenne muscular dystrophy (DMD) was first clearly delineated by Edward Meryon in 1851 but eponymously associated with Duchenne whose involvement was several years later.¹ But though the clinical details were well defined by the early 1960s, when my interest in the disease first began while pursuing post-graduate research at Johns Hopkins Hospital in Baltimore, the mode of inheritance was not clear. Sex linked inheritance seemed likely because the disease only affected boys. Furthermore, Walton described a severely affected woman in a family with affected men and postulated she might only have one X chromosome.² In fact, she did prove later to have XO Turner's syndrome. What was really required was a large extended family with the disease for linkage studies with known X linked markers—namely, colour vision and the recently described Xg blood group.

In 1961, Dreifuss and Hogan described a large family in Virginia with muscular dystrophy which, at the time, the authors considered to be a benign type of DMD.³ Fritz Dreifuss was then associate professor in neurology in the School of

UNUSUAL TYPE OF BENIGN X LINKED MUSCULAR DYSTROPHY⁴

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Medicine, University of Virginia. When I contacted him he was delighted and encouraged me to study the family—after all, his main interest was epilepsy where he would later become a world authority.

In those days you could pursue a great deal of research single handedly without the involvement of others, so I packed my car with all the equipment I thought necessary, including blood sampling equipment (for Xg studies), colour plates, a spectrophotometer, chemicals for creatine kinase assays (then known to be significantly raised in the disease) and an electrocardiogram machine to study cardiac function. Armed in this way I travelled on a Friday the several hundred miles south to the small hamlet in Virginia where the family originated, Dreifuss having arranged for my visit. I was met by the affected propositus who was a middle aged school teacher! This was clearly not the DMD I expected. That evening the school teacher and I spent a very enjoyable evening discussing the family and listening to his recordings of local folk music handed down from one generation to the next—one concerned with 'Queen Bess', Elizabeth I of England.

Early the following morning, the members of the family, affected and unaffected men as well as apparent female carriers (heterozygotes), all assembled in the schoolhouse, and throughout the day until late evening I carried out all of the various tests and investigations. On the following day after church, family members I had not seen assembled for me to complete my studies. I returned to Baltimore that evening totally exhausted but satisfied that I had all the information I required.

On analysing the data it was clear from the results that the X linked markers in the family were uninformative. But the clinical and ECG findings revealed an apparently distinct disorder with clear features:

- ▶ Early contractures of the elbows and Achilles tendons and later posterior cervical muscles often *before* there was any significant weakness.
- ▶ Slowly progressive muscle weakness predominantly proximal (scapulo-humeral) in the upper limbs and distal (anterior tibial and peroneal) in the lower limbs, at least at the beginning.
- ▶ No calf pseudohypertrophy.
- ▶ Myocardial involvement with cardiac conduction defects, an important feature, ranging from sinus bradycardia, prolongation of the PR interval and eventually complete heart block.

I included the details in my PhD thesis in 1964. I then returned to the UK and published the findings in *JNNP* in 1966. Studying a similar disease in other families in 1979, Rowland suggested the term 'Emery–Dreifuss muscular dystrophy' for this distinctive disease.⁵ I revisited the family 25 years later and recorded changes in the progress of the disease in affected members over the intervening period.⁶

Subsequent studies revealed that the gene locus for this disease was located at Xq28. The gene (*STA*) was later identified and shown to encode a nuclear membrane protein which Bione *et al* in Italy called 'emerin'.⁷ An autosomal dominant form of this disorder was later recognised, which is clinically similar to the X linked form. The gene for this disorder has been localised to 1q21 where the *LMNA* gene encodes another nuclear envelope protein, lamin A/C.⁸ Later research revealed that different mutations at this locus were associated not only with autosomal dominant Emery–Dreifuss muscular dystrophy but also with a rare autosomal recessive form of the disease as well as with a great variety of other conditions, including limb girdle muscular dystrophy

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1B, Charcot–Marie–Tooth neuropathy 2, mandibuloacral dysplasia and cases of progeria.⁹

The occurrence of these various mutations associated with such different phenotypes and the involvement of nuclear membrane proteins is generating much research but few clear answers have yet emerged.

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