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Early neurodevelopmental assessment in Duchenne muscular dystrophy

Marika Pane [a], Roberta Scalise [a], Angela Berardinelli [b], Grazia D'Angelo [c], Valeria Ricotti [d], Paolo Alfieri [e,f], Isabella Moroni [g], Louise Hartley [h], Maria Carmela Pera [b], Giovanni Baranello [g], Michela Catteruccia [e,f], Tiziana Casalino [g], Domenico M. Romeo [a], Alessandra Graziano [a], Claudia Gandioli [g], Flaviana Bianco [a], Elena Stacy Mazzone [a], Maria Elena Lombardo [a], Mariacristina Scoto [d], Serena Sivo [a], Concetta Palermo [a], Francesca Gualandi [i], Maria Pia Sormani [j], Alessandra Ferlini [i], Enrico Bertini [e,f], Francesco Muntoni [d], Eugenio Mercuri [a,d,*]

[a] *Department of Paediatric Neurology, Catholic University, Rome, Italy*
[b] *Child Neurology and Psychiatry Unit, IRCCS "C. Mondino" Foundation, University of Pavia, Italy*
[c] *IRCCS Eugenio Medea, Bosisio Parini, Italy*
[d] *Dubowitz Neuromuscular Centre, Institute of Child Health, University College, London, UK*
[e] *Child and Adolescence Neuropsychiatry Unit, Department of Neuroscience, Bambino Gesù Hospital, Rome, Italy*
[f] *Department of Laboratory Medicine, Unit of Molecular Medicine, Bambino Gesù Hospital, Rome, Italy*
[g] *Myopathology and Neuroimmunology, Pediatric Neurology and Neuroradiology Units, Neurological Institute C. Besta, Milan, Italy*
[h] *Department of Child Health, University Hospital Wales, Cardiff, UK*
[i] *Section of Medical Genetics, Department of Experimental and Diagnostic Medicine, University of Ferrara, Italy*
[j] *Biostatistics Unit, Department of Health Sciences, University of Genoa, Italy*

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Abstract

The aim of this study was to assess neurodevelopmental profile in young boys affected by Duchenne muscular dystrophy and to establish the correlation between neurodevelopmental findings, and the type and site of mutations. A structured neurodevelopmental assessment (Griffiths Scale of Mental Development) was performed in 81 DMD boys before the age of four years (range: 7–47 months). The mean total DQ was 87 (SD 15.3). Borderline DQ (between 70 and 84) was found in 32% and DQ below 70 in 12.3% of the patients. Children with mutations upstream or in exon 44 had higher DQ than those with mutations downstream exon 44 which are associated with involvement of dystrophin isoforms expressed at high levels in brain. The difference was significant for total and individual subscale DQ with the exception of the locomotor subscale. Items, such as ability to run fast, or getting up from the floor consistently failed in all children, irrespective of the age or of the site of mutation. Our results help to understand the possible different mechanisms underlying the various aspects of neurodevelopmental delay, suggesting that the involvement of brain dystrophin isoforms may cause a delay in the maturation of coordination and dexterity.

Keywords: Duchenne muscular dystrophy; Griffiths Mental Scales; Cognitive

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked disorder due to the lack of dystrophin, a subsarcolemmal protein. The disease is characterized by progressive weakness and wasting of skeletal muscles and, from the

* Corresponding author. Address: Department of Child Neurology, Policlinico Gemelli, Largo Gemelli, 00168 Rome, Italy. Tel.: +39 06 30155340; fax: +39 06 30154363.
E-mail address: mercuri@rm.unicatt.it (E. Mercuri).

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second decade, cardiac and respiratory impairment [1]. Cognitive and behavioral difficulties have been found in approximately a third of DMD patients [2–6] and are more frequent in patients with mutations after exon 44, affecting Dp 140, the short isoforms of dystrophin expressed in the brain, and are compounded further in boys with mutations towards the 3' end of the gene (after exon 63) affecting the shortest Dp 71 isoform, expressed at high levels in the brain [2–6].

With few exceptions [7–10], little has been reported about cognitive abilities in the first years or, more generally, on the early aspects of neurodevelopment. In younger children, especially below the age of two years, cognitive, motor and emotional aspects are strictly intertwined and these are better captured using neurodevelopmental scales. While a few studies have focused on specific aspects of neurodevelopment, such as locomotor [9] or language milestones [8], others have used neurodevelopmental scales but the cohorts were relatively small or also included children up to age of six years [7–10]. Furthermore, none of the previous studies [7–10] has so far explored possible correlation with site and type of mutations in this age group.

The restricted number of prospective studies is mainly due to the age at diagnosis which is still on average above the age of four years [11]. Although the first signs of concern can often be backdated to the second year of age, when DMD children show some signs of developmental delay and inability to develop new motor abilities such as running fast or jumping, the diagnosis is on average performed much later [11].

The aim of this study was to assess a cohort of young DMD boys by using a structured neurodevelopmental assessment (Griffiths Scale of Mental Development) in order to explore the spectrum of abilities in various neurodevelopmental domains. We were also interested to establish if, as observed in older boys, the neurodevelopmental profile was associated with type and site of mutations.

2. Subjects and methods

The study is a prospective multicentric study involving five tertiary neuromuscular centers in Italy (Catholic University and Hospital Bambino Gesù, Rome; IRCCS "C. Mondino" Foundation, Pavia; Neurological Institute C. Besta and Bosisio Parini Foundation, Milan) and two in United Kingdom (Dubowitz Neuromuscular Centre, London; University Hospital of Wales, Cardiff). Children were included if they were younger than four years and had a genetically proven DMD diagnosis or absence of dystrophin on muscle biopsy. In all patients genetic analysis, searching for exons deletions and duplication was performed using MLPA. In patients lacking DMD deletions and duplications, all 79 exons and the adjacent introns were analyzed through PCR amplification and direct sequencing. Mutations were named according to the Leiden muscular dystrophy database (http://www.dmd.nl/) using the nomenclature system published in 2000 in Human mutation.

2.1. Neurodevelopmental assessment

Neurodevelopmental outcome was evaluated by chartered psychologists and child psychiatrists using the Griffiths Scale of Mental Development. The scale

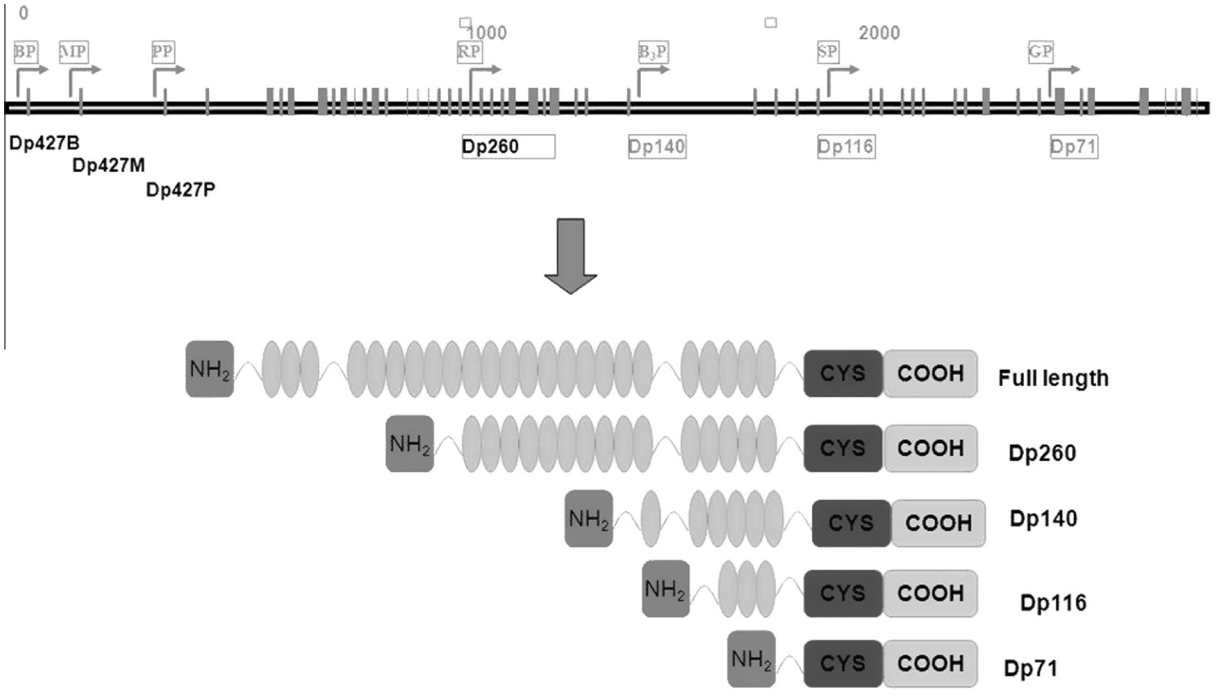

Fig. 1. Different isoforms of dystrophin.