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## High ck (creatine kinase) at Birth. Early Diagnosis of Duchenne Muscular Dystrophy (DMD) in two Premature Twins. Is it Time for the Newborn Screening?

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### Abstract

This is the report of an occasional diagnosis of DMD at the birth of two premature twins, took place through the detection of very high CK that directed towards confirmation via specific genetic test. The two children were transported to a specialized center after genetic counseling with parents and were included in a clinical trial program. We think this report is significant: it takes into account the need for screening in order to get an early diagnosis of DMD. Presently, it represents the most important challenge in approaching the pathology since it significantly improves the prognosis and doubles the life expectancy. This is due to the availability of therapies which are much more effective, if started in the pre-symptomatic phase: some of them were already in use with encouraging results while promising others are under study.

**Keywords:** Duchenne Muscular Dystrophy, neonatal screening test, early diagnosis**Abbreviations :** DMD: Duchenne Muscular Dystrophy; CK: Creatine kinase; MLPA: Multiplex Ligation Probe Amplification; NST: Neonatal Screening Test; FDA: Food and Drug Administration; NF-Kb: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated b Cells

### Background

DMD affects 1/3,500 male births per year. It is an X-linked recessive disease, in which the muscle damage is provoked by the absence of dystrophin, which is secondary to mutations in the DMD gene (Xp21.2). The diagnosis is suspected based on the clinical picture, family history and laboratory tests (CK is 100-200 times higher than normal levels) and is confirmed by genetic testing [1]. DMD must be considered in infants with delayed motor milestones, difficulty with jumping, running, climbing steps and rising from the floor, positive Gowers' sign, abnormal gait, muscle pains, calf hypertrophy, unexplained elevated liver enzymes, learning difficulties, behavioral problems, or speech and language delay. The onset of muscle weakness is typically in early childhood (at age 2 to 3) starting with the lower limbs. The complete absence of dystrophin is detected through a muscle biopsy [2].

In the past, few patients survived without intervention

beyond the second decade of life, but nowadays, improved care, in particular cardiac and ventilatory interventions, has dramatically increased life expectancy [3-7]. Despite substantial progress in DMD diagnosis and management, and increased accessibility of genetic testing, in many states the average age at which diagnosis takes place is still 4-5 years. In the UK the mean age of diagnosis is currently around 4.3 years of age and remained fairly static over the past 30 years [8]. In Italy it was estimated at 10 months in a study carried out between 2005 and 2014. The earliest diagnoses occur (up to 53% of cases) [9] following the occasional detection of high CK values, a biomarker of membrane fragility and muscle degeneration, during routine tests or before a surgery. The later the disease is intercepted, the faster the evolution towards severe disability occurs, while early multidisciplinary treatment allows to improve general conditions doubling life expectancy [10-12]. A preventive intervention at an early age is crucial, based on the early and seemingly non-reversible nature of the fibrotic tissue changes.

### Case Presentation

Males twins, born at 35 weeks of gestational age by C-section from bigemine, bicorial, biamniotic pregnancy from mother with a previous stillbirth at 25 weeks. Birth

weight of 2660 grams for the first born and 2775 grams for the second one. No neonatal resuscitation and regular postnatal adaptation. Physical examination was without pathological or noteworthy signs. Given the prematurity, the biochemical panel was done in a routine clinical-metabolic evaluation on the second day of life, with the detection of very high CK values (>14000 U/l) subsequently stabilized in the following days at levels of 8534 U/l and 6791 U/l, and hypocalcemia (7.4 mg/deciliter). Other tests were normal. In suspected neuromuscular disorder, genetic counseling for genomic rearrangements of the DMD gene by means of MLPA was requested. The deletion was identified, for both newborns, in hemizygosis of exons 46-55 of the dystrophin gene with resultant diagnosis at 4 days of life of DMD. The communication of the unexpected diagnosis was a particularly hard moment for the parents, but the genetic counseling were very useful and the two babies were sent to a specialized center and included in a clinical trial program.

### Discussion and Conclusion

Early diagnosis enables parents for informed making decisions concerning family planning and can offer access to advanced discussions and clinical tests. Some innovative clinical trials are based along the technology ASO, exon-skipping antisense oligonucleotides. At least three of them focus on the systemic gene-therapy availing of a micro-dystrophin gene; in one instance the study starts at 3 months of age [3]. In fact, early diagnosis translates into significant opportunities with prompt interventions before the muscle damage occurs, as easily as in the possibility of taking part in clinical tests that should begin as soon as possible, when the muscle tissue still retains its ability to self-renew; it also means early genetic counseling to parents which will be useful for successive pregnancies.

Early identification of the disease, also facilitates the communication of the diagnosis, understandably devastating for families, even harder for twins, with messages of greater encouragement and hope, necessary for the subsequent clinical course and to prevent distressing diagnostic odyssey. We believe that Neonatal Screening Test (NST) studies are essential because asymptomatic patients must be detected and treated benefitting from the opportunity to slow down the disease progression, consequently reducing morbidity and mortality and for the identification of therapies that are more effective when early started [13-15]. Besides a severe muscle phenotype, cognitive impairment and neuropsychiatric symptoms are prevalent. Mounting evidence links these symptoms to the loss of dystrophin in the brain. Even these symptoms are positively affected by early interventions and therapy [16].

A full scope of other drugs dedicated to DMD patients has been developing and been assessed in clinical trials, including strategies to rectify the underlying genetic cause of the disease, gene therapy, and non-mutation-dependent strategies including repurposing of existing drugs. For various years, research with oligonucleotides has been concentrating on correcting the splicing operation. Most of the mutations that cause Duchenne affect the exons, so as to alter the reading pattern of the dystrophin gene with a damage that blocks the production of the functional protein. The correct reading pattern of the gene can be restored by directly, eliminating, through the modulation of the splicing mechanism, an exon that is located near the region in which the mutation is present [17].

This is how eteplirsen, an FDA approved drug, acts by eliminating exon 51. It is mentioned to as "exon skipping", and induces the formation of partially functional dystrophin in about 13% of kids with Duchenne dystrophy. Eteplirsen is an RNA oligonucleotide (called antisense oligonucleotide) that by binding to the pre-mRNA prevents exon 51 from being included in the mRNA and favours its elimination. In this manner, a shorter but functional version of the protein is made [18]. In December 2019, FDA approved also golodirsen to treat DMD patients with a confirmed mutation amenable to exon 53 skipping (approx. 8% of DMD community) [19].

Ataluren is a mutation-specific therapy, a protein restoring agent, conceived to allow the formation of a functioning protein in patients suffering from genetic disorders caused by a nonsense mutation, suitable for approximately 10-15% of the DMD population. Primarily indicated in 2014 for DMD patients aged  $\geq 5$  years with nonsense mutation, the intake of ataluren has been extended by EMA in 2018 to 2-year-old patients [19].

Tamoxifen, Idebeneone [20-22] and Iterna are used to improve overall muscle function. Innovative steroids and NF- $\kappa$ B inhibitors are being looked into as possible alternatives to corticosteroids, aiming at keeping up their efficacy while reducing or avoiding the side effects connected with traditional corticosteroid [20-25].

Definitely, the most important challenge besides the therapy is the early diagnosis; and our case, never described previously, is a case in point which probably suggests the usefulness of a screening test at birth with the simple dosage of CK (simple, cheap, with a high sensitivity to DMD and fast results).

False positives, lack of efficient drugs and reliability about screening efficacy have hindered for many years a proper newborn screening for DMD. The availability of many

therapies, the diagnostic delay of DMD and the forthcoming new drugs make it necessary to meet stakeholders for the aims of identifying best practices concerning the DMD screening. A big heap of enthusiasm has spread recently amongst clinicians and patients associations. In China, Zhejiang, and Australia, pilot NST studies are being done in order to find the optimal time, whether 24-96 hours, 6-7 days or 6-12 weeks of age. [26] In Europe, the overall situation concerning NST differs quite considerably: 5 cases in France, 9 in UK and 14 in Germany. In Sweden, Finland, Hungary and Poland indeed 22-26 diseases get compulsorily screened at birth. Italy is a leader in Europe thanks to the detection of more than 40 diseases through the newborn screening. In no country DMD is included. DMD patients and their parents argued in favor of NST. NST diagnosis positively contributed to improve the quality of life of children and families and the high expectancy towards the diagnosis revealed no negative impact at psycho-social level [27, 28]. We have entered an unprecedented era in DMD research with an a forementioned new drugs entering the market that can restore dystrophin expression in the muscle and we can't miss this opportunity because of the diagnostic delay

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