D-Brain

Defining outcome measures for behavioural and emotional problems in dystrophinopathies

Hub Summary

Research has shown that in a proportion of individuals with DMD and BMD, there might be some involvement of how the brain works. This can result in some individuals having a degree of learning difficulties, behavioural or psychological difficulties.

To investigate this, we are conducting a large cohort study to identify which part of the DMD gene is responsible for the development of these complications and help us further define and develop robust clinical assessments which will outline psychological profiles for DMD and BMD patients.

The study will involve two consecutive visits, which will include assessment of cognition (thinking and problem solving) and behaviour (inattention, anxiety, hyperactivity, etc.) . These two visits will be repeated after 6 months. For those interested there is also the possibility of participating in the MRI component of the study.

This study will cover your travel expenses and will provide you with detailed feedback on your son's potential difficulties that can be used to receive educational support, to get a referral for local authorities or for your own personal use as it might give you some useful insights about your son's behaviour.

Study Number:

Description by UCL GOS Institute of Child Health

Duchenne Muscular Dystrophy is characterised by out-of-frame gene deletions that abolish the ability to produce dystrophin in muscles and in the brain. Studies have shown that brain dystrophin deficiency results in a neuropsychiatric syndrome in more than 50% of patients and have indicated higher incidence of neurobehavioural comorbidities such as Autism Spectrum Disorders (ASD), Attention Deficit Hyperactivity Disorders (ADHD), Obsessive Compulsive Disorders (OCD), Anxiety Disorders and Depressive disorders. These central nervous system (CNS) manifestations of DMD have major implications for the quality of life of the individuals affected. The milder allelic variant Becker Muscular Dystrophy (BMD), is associated with less severe progression of muscle weakness; individuals also experience brain comorbidities but their prevalence and severity in BMD has never been systematically assessed.

It is possible to restore brain-expressed dystrophin through intrathecal administration of antisense oligonucleotides (AONs) in mice, leading to reversal of the neurobehavioural phenotype. This implies aspects of the human neurobehavioural phenotype could be improved in DMD patients following dystrophin restoration in the brain. Clinical trials in boys with DMD are currently being conducted to improve skeletal muscle functioning in DMD, using exon skipping to restore the mRNA reading frame. AONs introduced into the CNS could potentially improve cognitive, behavioural and emotional symptoms associated with DMD and BMD, many of which are believed to result from brain dysfunction secondary to the genetic anomaly. Evaluating the effectiveness of treatment in a clinical trial demands robust clinical outcome measures, including biomarkers of the neurobehavioural phenotype.

The aim of this study is to develop a set of biometric outcome measures that are appropriately sensitive to change, for use in future clinical trials designed to improve neurobehavioural and neurocognitive functioning in DMD/BMD.

Primary Outcome Measures

1. Group differences between DMD, BMD and controls in the initial emotional response stimulus of the relevant task

Secondary Outcome Measures

1. Group differences between and within groups regarding learning, habituation and extinction in the emotional response task

2. Group differences between groups for the cognitive, behavioural and fine motor skills tasks

3. Group differences between groups for the MRI scans

Can I take part?

Inclusion Criteria

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DMD patients:

1. Male
2. Age range 7-17 years

Trial Status
Trial complete

UK Locations
London - GOSH, Trial complete/terminated

Trial Sponsor
UCL GOS Institute of Child Health

Length Of Participation
4-day visits (2 days initially followed by another 2 days at 6 months follow up)

Recruitment Target
100

Ambulatory
Ambulant and non-ambulant

Age
7-17 years

Mutation Specific
Mutation specific therapies, A genetic mutation that decreases expression of Dp427 alone (assigned to BMD Group 1), of both Dp427 and Dp140 (assigned to BMD Group 2)

Muscle Biopsy
No Muscle Biopsy Required

MRI
Yes

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3. A genetically proven diagnosis of DMD.
4. A genetic mutation that abrogates expression of Dp427 alone (assigned in DMD Group 1: Dp427-/Dp140+) or both Dp427 and Dp140 (assigned to DMD Group 2: Dp427-/Dp140-).

BMD patients:

1. Male
2. Age range 7-17 years
3. A genetically proven diagnosis of BMD.
4. A genetic mutation that decreases expression of Dp427 alone (assigned to BMD Group 1), of both Dp427 and Dp140 (assigned to BMD Group 2).

Control participants:

1. Male
2. Age range 7-17 years.

Exclusion Criteria

DMD & BMD patients:

1. Significant visual or hearing impairment
2. Specific phobias or sensory sensitivities to stimuli similar to the ones used in this study
3. Current participation in a clinical trial investigating a new drug involved in dystrophin modulation.
4. Inability to consent (for parents/guardians or self-reporting participants aged 16 and 17) or assent. This will exclude the rare individuals with extremely severe learning disability, as the assent in these patients is impossible (or the consent in self-reporting participants aged 16 and 17).

Control participants:

1. Significant visual or hearing impairment
2. Specific phobias or sensory sensitivities to stimuli similar to the ones used in this study
3. Any diagnosis of neurological or psychiatric condition

General exclusion criteria for MRI:

1. Claustrophobia
2. Pacemakers and defibrillators
3. Nerve stimulators
4. Intracranial clips
5. Intraorbital or intraocular metallic fragments
6. Cochlear implants
7. Ferromagnetic implants (e.g. thoracic implant for scoliosis)
8. Inability to lie supine during less than 45 minutes
9. Not having a general practitioner
10. Severe learning disability which will require a general anaesthetic

For contact details and to find out more, please refer to dmdhub.org.

Duchenne UK

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