Duchenne and the brain; **What is known from animal models?**

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WHAT IS KNOWN FROM ANIMAL MODELS?

Besides the well-known function of dystrophin in the muscle, there are also dystrophin variants that present in the brain. Up to 50% of DMD patients has cognitive and/or behavioural issues. A wide spectrum of disorders is seen. They may have a lower IQ (~30% of patients), learning difficulties (~25%) and memory impairments (~40%). Furthermore, ADHD (10-30%), autism (5-15%), obsessive compulsive disorder (5-60%) and anxiety (~30%) are common. Several patients also suffer from epilepsy (6%). These problems are more often seen in BMD patients too. Next to the genetic defect itself, other factors also affect behaviour, for example medicines like corticosteroids. There is a lack of attention to these cognitive and behavioural issues, while they can have a great impact on the life of the patients and families.

Dystrophin mutations and brain involvement

Multiple variants (called isoforms) of the dystrophin protein exist. The full-length protein (called Dp427) is present in muscle. There are, however, shorter forms of the protein that are found in several parts of the brain. The full-length Dp427 isoform is mainly found in the hippocampus (playing a role in memory, learning and emotions), the amygdala (emotions) and the prefrontal cortex (cognitive and social behaviour). A shorter form (Dp140) plays an important role during the development of the brain. Dp71 is present in all parts of the brain.

Which forms of dystrophin are missing depends on the specific mutation of the patient. The more distal the mutation the more isoforms are missing. It has been seen that cognitive and behavioural issues are mostly seen in patients also missing the brain forms Dp140 and Dp71. The absence of Dp71 leads to severe intellectual disabilities, but there are few patients (~5%) that miss this variant.

Studies in animal models

The *mdx* mouse is a mouse model in which the dystrophin protein is missing due to a mutation in the genes. This is the best studied animal model of DMD. There are several variants of this mouse model. Some of these lack next to the muscle variant, also other variants of the protein, like the ones present in the brain. These mouse models are very useful to study the role of dystrophin in the brain. Although it has not extensively studied yet, several brain and cognitive/behavioural abnormalities are seen in these mice too. Several of these seem to worsen with age. It is not clear whether this is also the case in patients.

Structural brain abnormalities
Using magnetic resonance imaging (MRI) it has been seen that the brain volume of these mice is reduced, structural changes are observed and that several of them have an aberrant shape of the skull. These changes become more prominent when mice get older. Indeed in a small part of DMD patients also changes in the brain structure and volume are seen, mainly in those which lack brain dystrophin isoforms.

Cognitive function
When mice are subjected to learning and memory tasks, they perform less then healthy mice. Mainly there long-term memory is impaired. This is already seen in mice that miss only the full-length isoform, but is more prominent in mice lacking other brain variants too.

Behavioural problems
Although not all behaviour issues seen in patients, can easily be studied in animals, several things have been observed by comparing their behaviour with animals that do not lack dystrophin. Anxiety can, for example, be tested by looking how they react to light (rodents are nocturnal animals, so prefer the dark). The mdx mice are indeed more anxious. Furthermore, they are more defensive and have a higher stress-level. This has also been seen in other animal models for DMD. In line with this, in a small study in patients also a higher level of anxiety has been seen.

Dystrophin isoforms and the brain
There has not yet been much research on the specific role of the different dystrophin variants in the brain. By comparing the mdx mouse that only lack the full-length Dp427 muscle variant with mdx mice that also miss the Dp140 brain variant, the effect of also missing this Dp140 can be studied. The main differences between these mouse models are seen in social behaviour, but learning, memory and anxiety are similar.

There is also a mouse model that only misses the short Dp71 isoform. These mice show similar behavioural changes to patients lacking this form. They have, for example, problems with their working memory, learning and are more anxious.

The effect of dystrophin restoration in the brain
First studies in mice show that restoring the expression of the full-length dystrophin in the brain may partly reverse the behavioural disorders, but it is too early to draw conclusions from these observations. It is for example not known to what extent the dystrophin level has to be restored to see improvements. They are now investigating whether restoring the Dp140 brain variant also has a beneficial effect on cognitive function and behaviour.

Future research

Since there is a lack of understanding concerning the role of dystrophin in the DMD brain and the consequences of this, a workshop has been held involving international experts to discuss the current knowledge. Plans have been made to further investigate its role, both in animal models and clinically in patients.

Psychosocial care for Duchenne patients

Cognitive and behavioural problems are often unrecognised (or too late) in DMD patients. Since these can have a great impact on the patients and their families, recognition and how to cope with them, is very important. Although the new care guidelines (published in 2018) recommend that psychosocial care should be part of the common care, screening for these disorders is not routinely done. It is also recommended that the care team includes a psychologist to support the families in coping with them.