

## POINTS OF VIEW

### MUSCLE EYE BRAIN DISEASE - A CASE REPORT OF COGNITIVE AND BEHAVIOURAL FEATURES

#### Introduction

*Muscle-Eye-Brain disease (MEB) is a disorder with an autosomal recessive inheritance characterised by congenital muscle dystrophy, eye and brain abnormalities (Cormand et al., 1999). The onset is usually in the first 6 months of life. MEB presents with marked delay in development resulting in severe or profound learning disability, epilepsy, hypotonia and muscular contractures. A high prominent forehead, protruding eyes and narrow temporal regions has been described as typical facial appearance of the disease (Santavouri et al., 1978). Until 2001, only 30 MEB patients were described worldwide, the majority of them from Finland (Fahnehjelm et al., 2001). Apart from the mention of severe or profound learning disability, there is no information on cognitive or behaviour phenotype of this rare disorder.*

#### Genetics and Pathogenesis

*MEB has autosomal inheritance and the gene responsible has now been assigned to a particular region in chromosome 1 (Cormand et al., 1999). The key to understanding MEB biology is a group of molecules in the muscle membrane called Dystrophin-Glycoprotein complex (DGC). This complex protects indi-*

*vidual muscle cells from damage as they stretch and contract. They also help to hold the cell in place by binding individual cells to extra-cellular matrix providing a bridge critical to muscle integrity. This complex has to be appropriately modified by an enzyme called Glycosyl Transferase to achieve this (Ross, 2002). The underlying muscle weakness and brain pathology in MEB disease is thought to be at this level (Michele et al., 2002). The link between this and the eye abnormalities however is still not understood.*

*The characteristic brain abnormality is type II Lissencephaly (cobblestone type) (Dobyns et al, 1985). While the normal cerebral cortex is divided into 6 distinct layers of cells, the cerebral cortex of patients with Lissencephaly has only 4 layers. It is an abnormality of brain development characterised by incomplete neuronal migration and smooth cerebral surface. Patients with Lissencephaly have severe or profound learning disability and often have epilepsy (Reiner and Lombroso, 1998).*

*Eye abnormalities in patients with MEB disease include: glaucoma (usually bilateral), pale optic discs, retinal hypoplasia, lens opacity and myopia. Myopia is the most consistent abnormality (Santavouri et al., 1978). Ophthalmologic assessment is important to aid diagnose and assess the progress of the disease in children with MEB disease (Fahnehjelm et al., 2001)*

Muscle dystrophy presents with severe muscle weakness and hypotonia. The muscle bulk is also significantly reduced. Santavouri et al. (1989) found that congenital muscle dystrophy was a consistent finding with the increased level of the enzyme Creatinin Phosphokinase (CPK). CPK is often raised 3-20 times the normal value, although it can be normal in some cases in the first year of life. The CPK remains elevated for many years. Delayed motor development, spasticity, and joint contractures are among other features of MEB.

## Case Report

This is the report of an adult with MEB syndrome focusing on the cognitive development and the behaviour. Mr. JB is a 27 year old man with MEB and severe learning disability. He is of Indian origin with one healthy sibling. There is no family history of developmental retardation or learning disability. He was born of a full term normal delivery.

### Motor Development

There was significant delay in motor milestones. He first held objects in his hand at 8 months, started to transfer objects at 11 month and rolled over at 13 months. Examination conducted when he was 10 months old showed hypotonia and generalised hypo-reflexia (weak reflexes). The loss of muscle power was more marked proximally than distally. An underlying muscle disease was suspected after he was found to have a raised Creatinin Phosphokinase level as well ( $>1000$  IU/L). At 5 years of age he started bottom shuffling, but flopped forwards when put in standing position. At the age of six, he was able to stand and walk with shoulders held, but was not able to play with toys meaningfully. At 9 years of age, he

was able to walk independently, although was still unsteady on his feet and was unable to manage stairs.

### Eye Manifestations

He was notice to have a squint at 4 months and an examination at 10 months revealed horizontal nystagmus and alternating convergent squint. Further investigation showed that he had myopia and bilateral pale optic discs with abnormal vascular entry. There was also bilateral salt and pepper pigmentation and a pre-retinal fold across the left optic disc. Electro Retino Gram (ERG) showed less than 50 microvolts in the left eye, suggesting severe visual impairment. Eye movements, however, appeared normal. He had recurrent episodes of uveitis (inflammation of the uvea) from the age of 7 years onwards. Ultrasound and electro-retinogram at about the same age showed evidence of retinal detachment in the left eye. At 11 years he was found to have severe myopia ( $-20$  dioptres in both eyes) with extensive posterior synechae (adhesions within the eye) in both eyes. He also developed a cataract in the left eye and ultrasound examination revealed total retinal detachment. Subsequently he lost vision in both eyes (12 years old). He was last seen in the eye clinic at 18 years of age, because he was poking his eyes constantly. Both eyes looked red, but there was no evidence of glaucoma and the intra-ocular pressure was normal in both eyes. Repeated poking was considered a form of self-stimulation as seen sometime in people with severe visual impairment.

### Epilepsy

At the age of 11 months he was found to be jerking from time to time, but was not treated for epilepsy. Myoclonic jerks were clearly iden-

tified when he was 13 years old and after a few months he developed tonic clonic and absence seizures. The EEG done at the time was normal. Although Carbamazepine was tried initially, it was withdrawn due to skin rashes. The epilepsy was then stabilised on Sodium Valproate. He now has mainly tonic and tonic clonic seizures, the frequency of which has increased in the last few years.

### **Cognitive development**

At 14 months he had an assessment using the Bayley scale (Bayley, 1969). This scale assesses early childhood development in three areas: mental, motor and behaviour. His overall performance was at a 6 months level showing marked delay in all areas. Language development assessed by the REEL scale (Bzoch and League, 1971) showed his communication to be at a 3-4 months level. This scale tests receptive, expressive and overall language and estimates age equivalent language in relation to these areas. Reassessment at the age of 2 years and 3 months using the Bayley mental scale (Bayley, 1969) showed his functioning at a 7-8 months level. Vineland Social Maturity Scale (Doll, 1965) revealed a social age of 7-8 months. The overall picture is that of a marked developmental delay in motor and mental milestones.

There are no objective assessments of his further development, but his parents report that he had made some progress in the areas of social functioning and mobility in the next four years. Although he never acquired speech, he was able to understand a few simple instructions and was able to move around. He then maintained this until he was 14 years old. Since the age of 14, there has been a progressive deterioration in his mobility, sleep and behaviour. A recent assessment using the Vineland Adaptive Behaviour Scales (Sparrow et al., 1984), revealed his overall mental age at

1 year and 1 month. His corresponding mental ages in the areas of communication, daily living skills, socialisation and motor are 1 year 4 months, 1 year 5 months, 11 months and 11 months respectively.

### **Behaviour**

About the age of 3 years, he had a tendency to bang objects making a loud noise. A psychologist, who had seen him at this time, suggested putting a padded surface in front of him or providing him with soft things, which would not make a noise when banged. At the age of 9 years, he was referred to child psychiatry service for poor sleep and screaming at night. He was making constant demands for his mother's attention at night. Behavioural interventions such as establishing routine, setting a regular bedtime with rapid settling and thereafter ignoring his cries for attention were tried with success.

When he was 14 years old he started banging his head. He would suddenly cry out and hit his head and face with his fists. When his arms were restrained, he would slip himself onto the floor and start banging on the floor. There seemed to be no immediate cause for his behaviour. He has been wearing two arm gainers holding his arms in full extension to prevent him from injuring himself. From the age of 14 years, he also got into the habit of punching his ears when frustrated. His ears, particularly the left, were blue and bruised most of the time. He also started to poke his eyes; he would do this until they were blood shot. Despite repeated assessment by specialists and investigations, no physical causes for these problems could be identified. It is clear that the onset of these self-injurious behaviours were associated with his loss of vision and mobility. These behaviours seem to have had a self-stimulatory function.

Subsequently he also developed episodes of

restlessness and hyperventilation. There would be an increase in the frequency of these episodes two or three days before he had a seizure when this would also be associated with an increase in the intensity of the self-injurious behaviours. A detailed assessment by the learning disability team revealed that the three main factors that contribute to these behaviours are epilepsy, infections (mainly chest, ear or urinary tract infections) and a lack of stimulation. Apart from the oral Diazepam, which is used when his agitation is severe to calm him down, he was not on any psychotropic medications. Although a small dose of Thioridazine was used successfully in the past, due to the increase in the severity of epilepsy and deteriorating physical health, Diazepam was considered to be safer. Diazepam is, however, effective only in relieving the restlessness that occurs in the pre ictal phase (immediately before the seizures). The overall management strategy relies on identification and treatment of any relevant physical problem (such as infections) at the earliest, management of epilepsy and providing a stimulating environment for the person. Different strategies are being introduced to provide him with tactile and auditory stimulation. Although these problems have not disappeared completely, the situation has certainly become more manageable with these interventions.

Increase in the intensity of epilepsy, infections and associated increase in self-injurious behaviour required frequent reviews and appropriate modifications in the management plan. Lack of information on the course of this rare disorder in adults is a particular problem in formulating a management plan as well as in counselling the carer.

## Discussion

MEB disease is a rare genetic disorder. It usually presents in the first 6 months of life

with a combination of congenital muscular dystrophy, eye defects, and brain abnormalities. The literature on the presentation of this syndrome is limited to the eye and muscle abnormalities and epilepsy. This case report highlights the cognitive development of an individual with MEB along with some of the behaviour problems that required psychiatric intervention.

There was a marked delay in his cognitive development from birth. He has severe/profound learning disability and a long-standing history of behavioural problems. There is a long-standing history of self-injurious behaviours such as head banging and poking the eyes. The main contributory factors for the self-injurious behaviours in this case are lack of appropriate stimulation, discomfort from physical problems such as infections and mood changes related to seizures.

This is the first report describing the cognitive and behaviour features of a person with MEB. The adolescent and adult years of people with MEB are marked by further deterioration of the disease. Although the main focus of the available literature is on the motor and visual impairment, change in the behaviour has been a main concern for the carers of this person with MEB. Lack of information on the nature and pattern of cognitive deterioration and behavioural problems cause difficulty in counselling and educating the carers. This highlights the need for further reports and studies on the behavioural aspects of MEB.

## Summary

Muscle-Eye-Brain disease (MEB) is an autosomal recessive disorder characterised by congenital muscle dystrophy, visual impairment, and brain abnormalities. Until 2001, only 30 MEB patients were described worldwide, the majority of them from Finland (Fahnehjelm et al., 2001). It usually presents in

the first 6 months of life with delay in milestone most marked in the area of motor development. Although people with MEB may live up to 40 years, survival is associated with further progression of this disease. A review of the available literature on the clinical presentation of this rare syndrome shows that the information is limited to the eye and muscle abnormalities and epilepsy. This case report highlights the cognitive development of a 27 year old man of Indian origin with MEB who has severe learning disability and epilepsy. There is a long-standing history of self-injurious and other behaviour problems as well.

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