Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Maternal homocystinuria and Moebius syndrome? Vascular aetiology

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Summary

A case of Moebius syndrome is reported in an infant of a mother known to have pyridoxine-unresponsive homocystinuria. The authors suggest that Moebius syndrome could result from early vascular insufficiency or disruption occurring early in development related to maternal homocystinuria.

Moebius syndrome consists of congenital complete or partial facial nerve palsy with or without paralysis of other cranial nerves and often in association with other malformations of the limbs and orofacial structures, but usually without gross structural brain abnormalities.

BACKGROUND

Moebius syndrome^{1–3} has not previously been described in an infant born to a mother with homocystinuria, and this association may lend weight to the theory of an early vascular insufficiency or disruption in the fetus as one of the possible aetiologies. In addition, the literature would suggest that most pregnancies to mothers with homocystinuria do not result in an abnormal baby and the greatest risk of the pregnancy is to the mother's health due to her heightened hypercoagulability; however this case report suggest that congenital abnormality in infant is possible.

CASE PRESENTATION

A female infant, birth weight 2755 g, was born at term by a normal vaginal delivery to a mother known to have pyridoxine-unresponsive homocystinuria. The pregnancy was unplanned and the mother complied poorly with her medications and diet. She had learning difficulties and suffered from depression. She was known to have high methionine levels. She had a history of a left subclavian thrombosis. She was on warfarin at conception which was changed to low molecular weight heparin during the pregnancy. She was also treated with betaine and folic acid. She suffered from asthma and was on flixotide, seretide and salbutamol. Antenatal scans demonstrated bilateral talipes, a ventriculoseptal defect and a possible coarctation of the aorta. An underlying syndrome was suspected. The mother was tested for myotonic dystrophy, which was negative. The mother had a long labour and was on an infusion of fentanyl. At delivery, the baby required resuscitation, thought at the time to be due to the maternal analgesia. Apgar scores were 2 at 1 min, 6 at 5 min and 9 at 10 min. She was intubated and ventilated initially and then required non-invasive respiratory support for 5 days. After delivery, she was noted to have a paucity of facial expression and uncoordinated swallowing in addition to the antenatally noted bilateral talipes. A diagnosis of Moebius syndrome was suspected clinically.

INVESTIGATIONS

A postnatal echocardiogram confirmed the presence of a VSD but excluded a coarctation. Genetic evaluation supported a diagnosis of Moebius syndrome. Chromosomes showed a normal 46 XX karyotype. The infant was negative for homocystinuria. An MRI of her brain showed a normal brain structure with a small volume right posterior fossa. Her hearing was normal.

OUTCOME AND FOLLOW-UP

A multidisciplinary team of speech and language therapists, neurologists, geneticists and orthopaedic surgeons was put in place for her ongoing management. She had severe gastro-oesophageal reflux and required nasogastric feeding. At 5 months of age she had a laparoscopic Nissen fundoplication and percutaneous endoscopic gastrostomy insertion.

DISCUSSION

The complete pathophysiology of Moebius remains unclear. The cranial nerves which may be involved include VI–XII, usually with sparing of VIII. Cranial nerves III and IV can also be involved but rarely. Cranial nerve VII is always involved, and VI, the abducens nerve, is involved in 75% of cases. In Moebius's original description of the condition, he considered there to be a degenerative or toxic process involving the nuclei of the affected nerves.^{4,5} It is quite likely that more than one aetiology can cause the features of Moebius syndrome. Approximately 2% of cases appear to have a genetic basis.⁶ Towfighi postulated four aetiological groups⁷ from neuropathological studies on 15 cases. Group I was characterised by hypoplasia of the cranial nerve nuclei from a primary congenital rhombomeric maldevelopment (sometimes referred to as the antegrade theory). Group II was characterised by neuronal loss and degeneration secondary to a defect in peripheral facial nerve (the retrograde theory). Group III was characterised by decreased neurons with degeneration, focal

necrosis, gliosis and calcification in the brainstem nuclei due to vascular insufficiency or infection. Group IV was characterised by a primary myopathy without lesions in the cranial nerves or nuclei. Similarly Verzijl *et al*,⁸ using electrophysiological studies in affected patients, found differing levels of abnormality from peripheral nerve, nuclear and supranuclear areas. They concluded that Moebius syndrome was a complex regional developmental disorder of the brainstem.

Supporting evidence that in at least some case a vascular disruption is important comes from the observation that mothers who take misoprostol in early pregnancy to induce uterine contractions and thus possibly disrupt the fetal blood supply in early gestation have 30-time greater risk, if the pregnancy continues, of having a baby with Moebius syndrome.⁹ Also, the use of cocaine with its potent vasoconstrictive effects has been implicated.¹⁰ Harbord *et al*¹¹ described a case associated with a unilateral cerebellar hypoplasia in which they postulated that a vascular disruption had occurred in the basilar artery early in development. The common association in Moebius syndrome of limb abnormalities, for example, talipes and Poland anomaly, would also suggest a disruption of normal morphogenesis during a critical period in the development of these embryonic structures at around 4–7 weeks of gestation.

Homocystinuria is an inherited metabolic disorder resulting from defects in either the remethylation or transsulphation pathways of homocysteine metabolism. Homocysteine is a sulphur-containing amino acid. Its metabolism depends primarily on the enzymes and various vitamin cofactors. Defects in its metabolism results in an accumulation of homocysteine and methionine in the blood. The biochemical imbalance causes a weakness of collagen linkage resulting in mental retardation, ectopic lentis, skeletal and connective tissue abnormalities resembling Marfan's syndrome. Homocystinuria also causes a hypercoagulable state with an increased risk of venous and arterial thrombosis as well as peripheral vascular disease risks. In pregnancy, homocystinuria in the mother is associated with repeated spontaneous abortions, pre-eclampsia, placental abruption, intrauterine growth retardation and intrauterine death.^{12–13} Other prothrombotic defects such as deficiencies of antithrombin, protein C or protein S and factor V Leiden are associated with similar pregnancy complications¹⁴ and it has been postulated that an impaired uteroplacental blood flow contributes to these outcomes. Neural tube defects have also been described in human infants born to mothers with homocystinuria¹²; related to abnormal myelin synthesis, and in mice a cerebellar pathology¹⁵ has been described. Mothers with homocystinuria have been shown to carry babies with high levels of homocysteine and methionine in the amniotic fluid¹⁶ and high levels of methionine and cystathionine in fetal tissue from early fetal life.¹⁷ The experimental evidence has suggested a role of hyperhomocysteinaemia in production of neural tube defect and cardiac defect. This is especially evident where the mother has coexisting hypermethioninaemia.

The mother in our case was on multiple other therapies. Of note, she was on Warfarin at conception but the embryotoxicity of Warfarin is well described and that our case did not demonstrate features of this would suggest

that the development of Moebius syndrome in the baby may represent another manifestation of abnormal placental blood flow at a critical period in early gestation related to the mother's poorly controlled homocystinuria.

The literature would suggest that most pregnancies to mothers with homocystinuria do not result in an abnormal baby,¹⁸ and the greatest risk of the pregnancy is to the mother's health due to her heightened hypercoagulability; however, caution, careful monitoring during pregnancy and assessment of the baby after delivery is warranted.

Learning points

- An early vascular insufficiency or disruption in the fetus should be considered as a possible aetiology of Moebius syndrome.
- Congenital abnormality in the baby is possible with maternal homocystinuria especially with coexisting hypermethioninaemia.
- Careful monitoring during pregnancy and assessment of baby postnatally is warranted in homocystinuria.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Gupta N, Anthony MY. Maternal homocystinuria and Moebius syndrome? Vascular aetiology. *BMJ Case Reports* 2011;10.1136/bcr.09.2010.3331, date of publication

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