Myasthenia gravis with antibodies to muscle-specific kinase : clinical characteristics, epidemiology, and immunological aspects

Niks, E.H.

VII

A transient neonatal myasthenic syndrome with anti-MuSK antibodies

E.H. Niks [1], A. Verrips [2], B.A. Semmekrot [2*], M.J.J. Prick [2], A. Vincent [3], M.J.D. van Tol [1§], C.M. Jol-van der Zijde [1§], J.J.G.M. Verschuuren [1]

From the Departments of Neurology, [*] Pediatrics and [§] Pediatrics, Section of Immunology, Hematology, Oncology, Bone Marrow Transplantation and Autoimmunity.
[1] Leiden University Medical Center, The Netherlands,
[2] Canisius-Wilhelmina Hospital Nijmegen, The Netherlands,
[3] Weatherall Institute for Molecular Medicine, John Radcliffe Hospital, University of Oxford, United Kingdom.

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Introduction

Some patients with myasthenia gravis (MG) have autoantibodies to muscle-specific kinase (MuSK) instead of the acetylcholine receptor (AChR). Anti-AChR antibodies may be transferred across the placenta causing a self-limiting neonatal myasthenic syndrome. We describe an infant with a similar disorder whose mother had MuSK MG.

Case report

In September 1994, the mother noticed unilateral ptosis and a feeling of generalised fatigue at age 13. Over the next months, she developed severe oculobulbar weakness, dyspnoea and weakness of the neck. Symptoms were fluctuating and unresponsive to acetylcholinesterase inhibitors. No antibodies to the AChR were found. In 1995, a normal thymus was removed. High doses of prednisone had little effect. In 1997, plasmapheresis induced a partial remission and this became her regular therapy for several years. In 2004 anti-MuSK antibodies were found. She had two first trimester miscarriages while using pyridostigmine and prednisone in September and December 2004. In May 2005, she became pregnant using only prednisone 20 mg on alternating days. This pregnancy was uneventful without large fluctuations of her myasthenic symptoms.

In February 2006, at 38+1 week of gestation, she unaidedly delivered a boy in head position. Apgar score was 10 after 1 and 5 minutes. Birth weight was 3190 gram (P25). Physical examination was unremarkable. After 8 hours, however, drinking became difficult. After 16 hours, he showed mild generalised hypotonia with diminished facial expression and a weak cry. Thirty-two hours after birth, examination showed paucity of general movements, a tent-shaped mouth and chest retractions. After 10 minutes of examination, weakness increased, leading to an immobile frog position (Figure 7.1). Tube feeding was initiated. Intramuscular neostigmine gave a temporary improvement of symptoms and oral pyridostimine 0.2 mg every 3 hours was started. On day 4, the amount of tube feeding could gradually be decreased. Quantities of spontaneously ingested bottle feedings increased from 5 mL on the 4th to 35 mL on the 8th and to 75 mL on the 13th day. On day 11, examination showed only a mild head lag. On day 15, he was discharged, spontaneously drinking his bottles of 7 times 80 mL. On day 22, neurological examination was unremarkable. Further growth and development were normal.

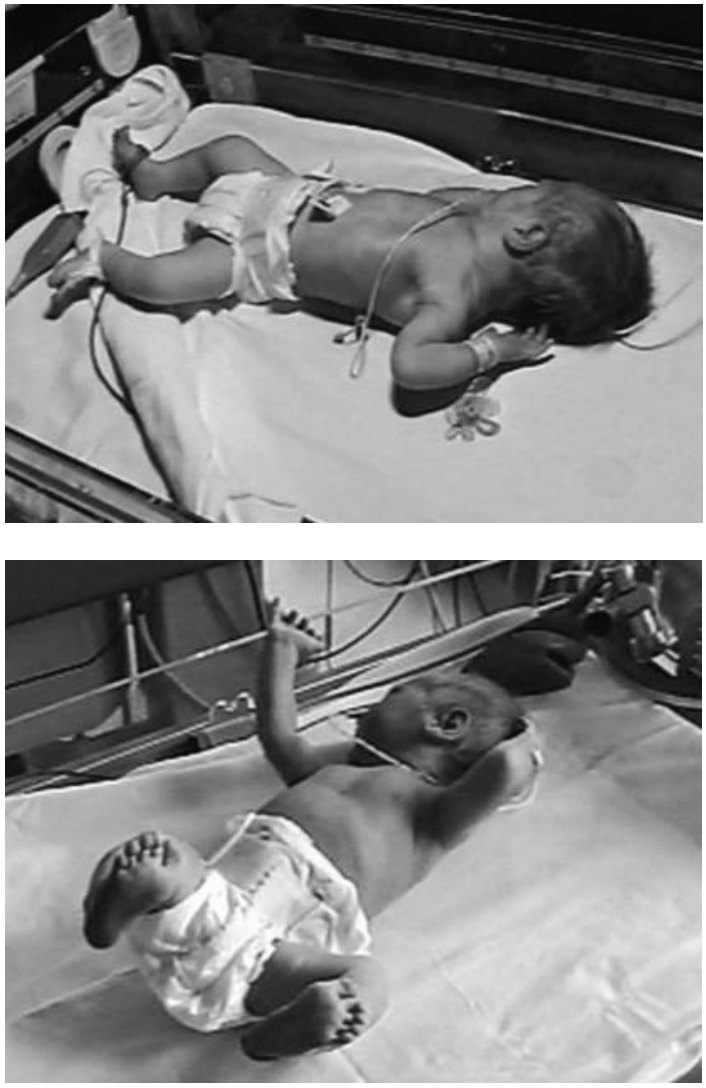

Figure 7.1 Neonatal myasthenic weakness on day 3 (top) and remission on day 6 (bottom)
On day 3 the infant shows severe muscle weakness lacking the power to overcome gravity. On day 6, normalisation of muscle strength was observed. Parental consent was obtained for publication.

Maternal and neonatal anti-MuSK specific IgG1 and IgG4 levels were measured by ELISA, [93] using monoclonal antibodies anti-Human IgG subclasses (IgG1, MH 161-1, Sanquin, Amsterdam, The Netherlands, and IgG4, NI315, Nordic, Tilburg, The Netherlands) and alkaline phosphatase (AP) labelled Rabbit anti-Mouse Ig (1:750, Dakopatts, Glostrup, Denmark). Total IgG anti-MuSK titres were measured using AP labelled Goat anti-Human IgG (Biosource, Camarillo, CA, USA). The ratio of MuSK-specific total IgG versus subclass

IgG in pooled sera from MuSK MG patients containing predominantly one anti-MuSK specific IgG subclass yielded a factor enabling direct comparison of IgG1 and IgG4 anti-MuSK titres in these patients (Figure 7.2).

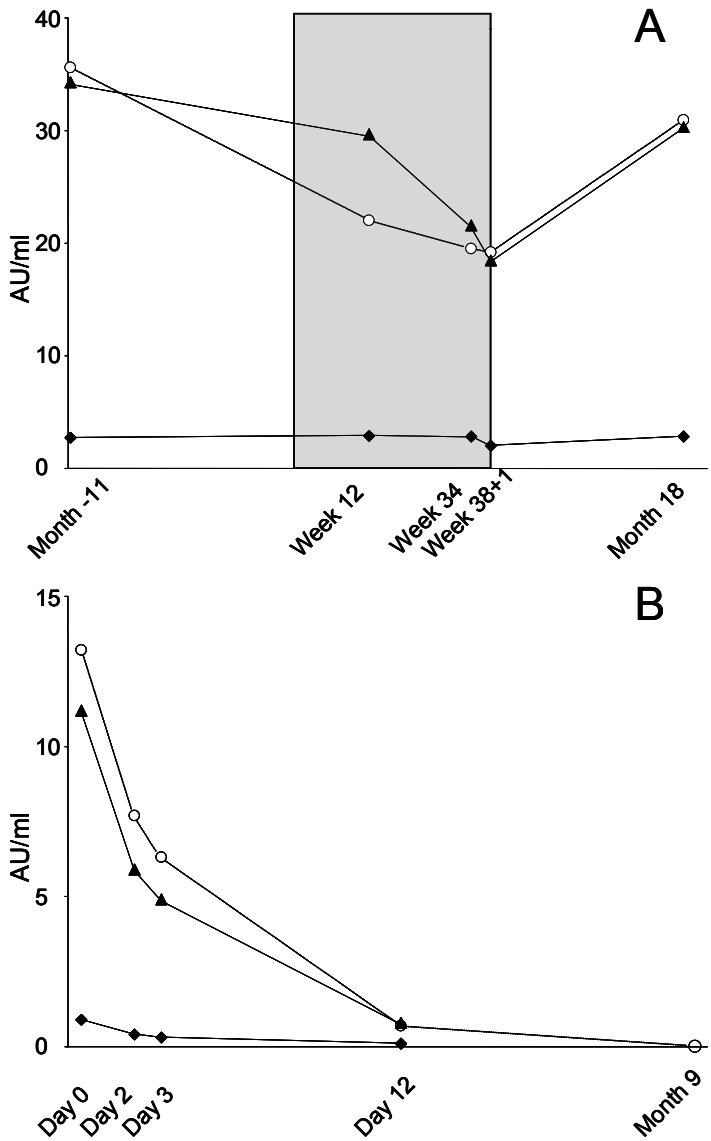

Figure 7.2 Course of maternal (A) and neonatal (B) titres of anti-MuSK specific IgG antibodies
Titres are expressed as arbitrary units per mL compared to an internal standard. The time scale is related to the day of conception (A) and the day of birth (B).
◯ = *total IgG,* ◆ = *IgG1,* ▲ = *IgG4,* □ = *Pregnancy*

Discussion

This case report shows that transient neonatal myasthenia gravis (NMG) is possible through cross placental transport of maternal anti-MuSK antibodies. The pathogenicity of the antibodies, that are mainly IgG4 in the patients presented here, is supported by the paralleled course of neonatal titres and clinical symptoms. NMG without anti-AChR antibodies has been described before the role of MuSK in seronegative MG became known. [50] In retrospect, anti-MuSK antibodies may have been involved in some of these patients. In AChR MG, 10 to 15% of the infants develop NMG although autoantibodies are transferred to nearly all infants. [152] Giving birth to an infant with NMG seems to enhance the risk of NMG in following newborns. [153] There are contrasting data whether the maternal anti-AChR antibody titre is predictive for the occurrence of NMG. Both healthy infants from mothers with high titres and affected ones from mothers with low titres have been described. [154,155] Active transport of IgG across the placenta favours IgG1 over IgG4, IgG3 and IgG2 and takes place from early in the second trimester. [156] The risk of NMG in IgG4 mediated MuSK MG could therefore be lower than in IgG1 mediated AChR MG. The delay between delivery and onset of symptoms is remarkable. Most probably, neuromuscular synapses have been exposed to maternal anti-MuSK antibodies in utero but the infant had an excellent start and fetal development was normal. In animals, extensive remodelling of synapses occurs in the weeks after birth and MuSK might play an essential role in this process. In view of the short symptom free period, one could also postulate the existence of a short lasting mechanism optimizing the first essential muscle contractions of the neonate, like an abundance of presynaptic acetylcholine or decreased acetylcholinesterase activity, counteracting the myasthenic effect of the antibodies. It should be noted that two earlier pregnancies ended in spontaneous abortions with unknown cause. Although these occurred in the first trimester, a pathogenic effect of anti-MuSK antibodies in utero cannot be excluded. In pregnant mothers with MuSK MG, fetal and neonatal development of the infants should be carefully observed.

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