

# Teratogen Update: Maternal Myasthenia Gravis as a Cause of Congenital Arthrogryposis

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## ABSTRACT

**Background:** Arthrogryposis multiplex congenita (AMC) is defined as nonprogressive congenital contractures that generally result from lack of fetal movement in utero. AMC is a feature of many congenital disorders caused by genetic, environmental, or other factors. One rare cause of AMC is maternal myasthenia gravis (MG). This is an autoimmune disorder, caused by antibodies to the nicotinic acetylcholine receptor (AChR), and resulting in weakness of voluntary muscles. In 10–15% of babies born to MG mothers, transient signs of MG are noted after placental transfer of anti-AChR antibodies. In a few cases, AMC predominates.

**Methods:** We review the role of antibodies to AChR in MG and in AMC associated with maternal antibodies to AChR.

**Results:** In anti-AChR antibody-associated AMC, fetal or neonatal death is common; other deformities or CNS abnormalities are common as well. The condition usually recurs in each pregnancy unless the mother is treated for MG, but some mothers are asymptomatic. The maternal antibodies cross the placenta and block the function of the fetal isoform of the AChR leading to fetal paralysis. Injection of maternal plasma into pregnant mice results in AMC in mouse fetuses. Some women with recurrent AMC in their babies have no detectable anti-AChR suggesting the presence of antibodies to other fetal muscle or neuronal proteins.

**Conclusions:** Although rare, anti-AChR-associated AMC is potentially treatable and can be diagnosed by a routine antibody test. The mouse model can be used to investigate the role of these and other maternal antibodies in causing congenital conditions.

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years of age among Caucasians. Infantile onset of MG is much more common in the Chinese paediatric population (Chiu et al., '87). Many Caucasian patients present in adolescence or early adult life, and these are most often female. MG is caused by serum antibodies binding to the nicotinic acetylcholine receptor (nAChR) on the postsynaptic surface of the neuromuscular junction, and which is essential for neuromuscular transmission. The antibodies lead to loss of nAChR, resulting in progressive weakness and fatigue of voluntary muscles (Drachman, '94). Anti-AChR antibodies are detected by radioimmunoassay (RIA, using <sup>125</sup>I- $\alpha$ -bungarotoxin-labelled AChR), and are very variable in titre. But within an individual patient the level of antibodies correlates well with disease status, and they are very rare (<1%) in healthy subjects (Vincent et al., '86). A small percentage of patients (10–15%) with a clinical diagnosis of MG do not have detectable anti-AChR in their serum (seronegative MG [SNMG]); this condition is probably due to antibodies directed at some other neuromuscular junction target (Blaes et al., '00).

The role of serum anti-AChR antibodies in MG was clearly demonstrated by passive transfer experiments in which injection of MG immunoglobulins (Igs) into experimental mice produced many of the symptoms and signs of MG (Toyka et al., '77). It was confirmed by a striking clinical response to plasma exchange and immunosuppressive treatment (Newsom-Davis et al., '78).

The thymus gland is involved in MG. Many patients, particularly those with onset of disease during adolescence or early adult life (early-onset MG), respond well to thymectomy, and about 25% do not need further treatment. The thymus gland is often hyperplastic in these cases, and secretes anti-AChR antibodies, per-

## MYASTHENIA GRAVIS

Myasthenia gravis (MG) is one of the best-characterised human immune-mediated disorders. The estimated incidence in the population is around 1:10,000. This acquired condition can present at any stage of life but is relatively rare in children and very rare before 2

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haps because the presence of AChR on muscle like cells in the thymic medulla stimulates specific B cells (Drachman, '94). Patients who do not respond to thymectomy may be given prednisolone or azathioprine, or a combination of both (Palace et al., '98).

**MATERNAL MG AND FETAL COMPLICATIONS**

Placental transfer of maternal anti-AChR antibodies to the fetus can cause transient neonatal myasthenia gravis (NMG) in about 10% of newborns of MG mothers (Namba et al., '70), although the incidence may be decreasing with improved treatment of mothers. At birth, or shortly afterward, babies present with hypotonia, respiratory distress, and feeding difficulties which usually resolve in 4–6 weeks. However, a more severe clinical spectrum can also occur; the death rate due to fetal anomalies is higher than in the general population (Batocchi et al., '99). Different systems and/or single organs may be involved, although arthrogryposis is one of the most frequent findings.

**CAUSES AND CLASSIFICATION OF AMC**

The term *arthrogryposis* (*arthron* = “joint,” *gryposis* = “bent”) is largely used in clinical practice to describe a variable sign recognisable in many different malformative syndromes. On the basis of clinical features, Hall ('96) proposed three different phenotypic patterns of arthrogryposis: (1) isolated; (2) associated with other systemic anomalies; and (3) associated with dysfunction and/or malformation of the central nervous system (CNS).

The first study that clearly demonstrated the importance of lack of fetal movement in causing arthrogryposis was conducted by Drachman and Coulombre ('62). These workers found that injection of curare into chick embryos resulted in multiple congenital contractures at birth. Jago ('70) reported the occurrence of arthrogryposis in a baby born to a mother with tetanus who had to be treated with muscle relaxants during pregnancy. Moessinger ('83) produced an animal phenotype characterised by fetal growth retardation, pulmonary hypoplasia, short umbilical cord, and multiple joints contractures by giving daily intrauterine injections of curare during the last days of gestation. The anomalies, which Moessinger called the “fetal akinesia deformation sequence,” bore a striking resemblance to the syndrome first described by Pena and Shokeir ('74) in four newborn infants.

Although a specific cause has not been established in many of the patients with AMC, five different pathogenic categories of arthrogryposis have been distinguished on the basis of the cause of the limitation of fetal movement:

1. *Neuropathic processes*: include either central (CNS) or peripheral nervous system (PNS) defects, or sometimes a combination of both (e.g., brain and spinal cord malformations, spinal muscular atrophy, amyelinating congenital neuropathy, nonprogressive congenital neuropathy)
2. *Myopathic processes*: pathologic conditions related to both the muscle and neuromuscular junction (congenital muscular dystrophy, congenital myasthenia), as well as primary amyoplasias
3. *Abnormal connective tissue disorders*: include joint and tendon abnormalities
4. *Physical constraints in utero*: (e.g., twin pregnancy, oligohydramnios, amniotic bands, or structural anomalies of the uterus)
5. *Maternal illness*: include maternal infections and maternal neurological conditions, which are occasionally associated with arthrogryposis, e.g., maternal rubella and varicella infection and some other infectious diseases (Hall and Reed, '82); maternal myotonic dystrophy, diabetes, hyperthermia, hypotension, multiple sclerosis, and MG (Smith et al., '78; Hall and Reed, '82; Farrell and McGillivray, '83; Livingstone and Sack, '85)

This review concentrates on AMC associated with MG in which there are maternal antibodies to AChR.

**AMC ASSOCIATED WITH MG**

Although neonatal MG is the most common problem seen in infants of mothers with MG, there have been cases reported with arthrogryposis. To date, 32 affected offspring born to 13 myasthenic mothers have been reported. The cases are summarised in Tables 1–4, where they are separated depending on whether the mother had MG at the time of the first pregnancy. In addition, one reported case in which the mother was entirely symptom free is detailed in Table 4. Several features emerge from analysis of the cases.

**Variable severity of AMC**

The severity of AMC in the infant is variable and does not relate to the severity of mother's MG, either at onset or at the time of the first or subsequent pregnancy. Strikingly, in those with poor outcomes, there were other features of the fetal akinesia sequence. Eight babies were stillborn, and nine died during the neonatal period. In these cases, there was often a history of reduced fetal movement and polyhydramnios. Postmortem studies showed findings compatible with fetal akinesia sequence but, in addition, a few cases had damage to the CNS. In some cases with less severe AMC, there was a mixed picture at birth and symptoms of neonatal MG. If they survived the neonatal period, the outcome was generally good.

**High recurrence risk of fetal deformities**

An important feature of these cases and a clue to the diagnosis in the family reported by Vincent et al. ('95) (Table 4) was the high recurrence rate. The mother was counselled originally for an autosomal recessive disorder but, after the fifth recurrence and, being aware of the family reported by Barnes et al. ('95), the geneticist

1. *Neuropathic processes*: include either central (CNS) or peripheral nervous system (PNS) defects, or sometimes a combination of both (e.g., brain and spinal cord malformations, spinal muscular atrophy, amyelinating congenital neuropathy, nonprogressive congenital neuropathy)

TABLE 1. AMC cases in which maternal myasthenia gravis was diagnosed before birth of the first affected offspring

Reference	Maternal clinical history	No. of pregnancies	Pregnancy 1	Pregnancy 2	Pregnancy 3	Pregnancy 4	Pregnancy 5	Treatment during pregnancies
Shepard ('71)	Age at onset of MG: 16 yr Anti-AChR: nr	2	MA: 24 yr Labour at 30 wk, stillbirth with AMC PM: pericerebellar subarachnoid haemorrhage, no other gross abnormalities	MA: 24.5 yr Labour at 29 wk, stillbirth with AMC and generalised subcutaneous oedema PM: normal				First pregnancy: pyridostigmine until 29 wk gestation
Pasternak et al. ('81)	Age at onset of MG: nr Anti-AChR: nr	1	MA: 28 yr hydramnios, neonatal MG, AMC, diaphoresis + cholinergic phenomena, positive anti-AChR Therapy: neostigmine + plasma exchange. Outcome: no long-term problems					Pyridostigmine
Moutard-Codou et al. ('87)	Age at onset of MG: 16 yr Anti-AChR: positive	5	MA: 28 yr Stillbirth at 28 wk with AMC, cleft palate, jaw agenesis, and spina bifida	MA: 28 yr Spontaneous abortion	MA: 29 yr Pregnancy complicated by hydramnios at 20 wk; stillborn twins born at 28 wk, no obvious abnormalities	MA: 30 yr Hydramnios from 22 wk Stillbirth at 29 wk with AMC and oedema PM: lung hypoplasia	MA: 34 yr Hydramnios from 27 wk with decreased fetal movements and finger contractures at 30 wk Born by caesarean at 33 wk Hypotonic finger contractures, ptosis, and poor respiration Anti-AChR: positive Successfully treated with artificial ventilation, pyridostigmine, and exchange transfusion	Not recorded
Eymard et al. ('89)	Age at onset of MG: nr Anti-AChR: nr	2	MA: nr Neonatal MG	MA: nr AMC, mild respiratory distress, Outcome: full recovery MA: nr; died at 36 hr PM: Lung hypoplasia, scoliosis, AMC				
Carr et al. ('91)	Age at onset of MG: 18 yr Anti-AChR: positive	3	No deformities, died soon after birth PM: adherent placental clots, marked lung hypoplasia		MA: nr Hydramnios at 32 wk, delivered at 35 wk Transient neonatal MG, requiring intermittent ventilation and anticholinesterase medication for 5 wk			First pregnancy: pyridostigmine + thymectomy Third pregnancy: pyridostigmine throughout, plasma exchange 15-17 wk, prednisolone 17 wk onward
J. Newsom-Davis (unpublished observations)	Age at onset: 28 yr Anti-AChR: positive	4	MA: 29 yr Hydramnios, fetal oedema, small chest, TOP. PM: hypertelorism, beak-shaped nose, small mouth, lung hypoplasia Muscle from all parts of the body showed marked chronic myositis	MA: 32 yr Normal until 18 wk Premature labour, AMC, large head, beak-shaped nose, small mouth, micrognathia, abnormal palate, narrow chest, pectus excavatum, scoliosis, abnormal genitalia	MA: 32 yr Preterm 28 wk, AMC; died 35 min after birth	Normal		After third pregnancy: thymectomy, intravenous IgG and plasma exchange

AMC, arthrogyposis multiplex congenita; AChR, acetylcholine receptor; MG, myasthenia gravis; nr, not reported; MA, maternal age; PM, postmortem; TOP, termination of pregnancy.

**TABLE 2. AMC cases in which maternal myasthenia gravis had been diagnosed but mother was symptom free during the affected pregnancies**

Reference	Maternal clinical history	No. of pregnancies	Pregnancy 1	Pregnancy 2	Pregnancy 3	Comments
Stoll et al. ('91)	Age of onset: 15 yr Anti-AChR: positive Therapy: pyridostigmine, thymectomy at 18 yr	2	MA: 23 yr Preterm, AMC, prominent occiput, small chin, funnel chest Anti-AChR: positive died at 1 hr PM: normal	MA: 26 yr AMC at ultrasound TOP at 20 wk PM: normal		
Tranchant et al. ('91)	Age at onset: 16 yr Anti-AChR: positive Therapy: pyridostigmine, neostigmine, thymectomy at 16 yr	3	Spontaneous abortion at 8 wk	MA: 23 yr Hydramnios, AMC on ultrasound with stillbirth PM: lung hypoplasia	MA: 25 yr AMC on ultrasound at 21 wk, TOP PM: retromicrognathia, AMC	Nil at time of pregnancies
Dinger and Prager ('93)	Age at onset: 19 yr Anti-AChR: positive Therapy: pyridostigmine, thymectomy at 20 yr	1	MA: 26 yr Hydramnios, AMC, hypotonia, severe respiratory distress, dolicocephaly, myopathic face, ptosis, scoliosis AChR ab positive Therapy: pyridostigmine Outcome: At 4 mo, facial diplegia, ptosis, swallowing difficult, hypotonia, AMC improved, mentally alert			Nil at time of pregnancy

AMC, arthrogyposis multiplex congenita; AChR, acetylcholine receptor; nr, not reported; MA, maternal age; PM, postmortem; TOP, termination of pregnancy.

TABLE 3. AMC cases in which maternal myasthenia gravis was diagnosed after the affected pregnancies

Reference	Maternal history	No. of pregnancies	Pregnancy 1	Pregnancy 2	Pregnancy 3	Pregnancy 4	Pregnancy 5	Pregnancy 6	Comments
Holmes et al. ('80)	Age at onset of symptoms: 17 yr MG diagnosed after the third pregnancy Anti-AChR: positive	4	MA: 22 yr Neonatal MG	MA: 27 yr No problems	MA: 29 yr Died at 14 hr AMC, syndactyly, short sternum, prominent occiput, cryptorchidism. PM: normal lung weight; anoxic changes in cerebellum and hippocampus	MA: 30 yr Fifth finger flexed; no other problems			After third pregnancy: pyridostigmine and thymectomy
Dulitzky et al. ('87)	Age at onset: adolescence; at 20 yr problem with anaesthetics MG diagnosed after delivery of third child Anti-AChR: positive Therapy: nr	3	Normal	Normal	MA: 26 yr Hydramnios, AMC, hypotonia, prominent metopic suture, hypertelorism, low-set ears, flat nasal bridge, micrognathia, high-arched palate, kyphoscoliosis, cryptorchidism Anti-AChR: positive Therapy: pyridostigmine Died at 37 days PM: normal				
Moutard-Codou et al. ('87)	Age at onset of MG: 26 yr Anti-AChR: positive	1	MA: 26 yr Pregnancy: hydramnios and decreased fetal movement Born at 36 wk AMC, facial diplegia, low-set ears, downward palpable fissures, plagiocephaly, swallowing difficulty, respiratory distress Anti-AChR: positive Outcome: facial diplegia						Not recorded

TABLE 3. (continued)

Reference	Maternal clinical history	No. of pregnancies	Pregnancy 1	Pregnancy 2	Pregnancy 3	Pregnancy 4	Pregnancy 5	Pregnancy 6	Comments
Barnes et al. (95)	History of anaesthetic problems after first pregnancy at age 24; weakness since then MG diagnosed after the fourth pregnancy. Anti-AChR: positive	5	MA: 24 yr Hydranmios, IUGR, AMC, small palate, low-set ears, receding forehead, cryptorchidism; death at 7 hr PM: lung hypoplasia + malsegmentation	MA: 25 yr IUGR at 37 wk Tachypnoea, sucking difficulty, Distal AMC Outcome: no long-term problems	MA: 26 yr Hydranmios, AMC, respiratory distress, scoliosis, mild hydronephrosis, cryptorchidism Died at 7 wk PM: lung hypoplasia, atrial septal defect, cerebral and cerebellar atrophy	MA: 27 yr AMC and absent stomach at 27 wk on ultrasound Preterm at 33 wk Died at 20 min	MA: 31 yr Intrauterine death at 17 wk; no obvious cause	MA: 33 yr Male infant born at 39 wk with mild pulmonary hypoplasia and fifth finger arthrogryposis No long-term problems	After fourth pregnancy: thymectomy, prednisolone, azathioprine and plasma exchange in subsequent pregnancies

AMC, arthrogryposis multiplex congenita; AChR, acetylcholine receptor; MG, myasthenia gravis; IUGR, intrauterine growth retardation; nr, not reported; MA, maternal age; PM, postmortem.

TABLE 4. AMC case in which mother had no symptoms or sign of myasthenia gravis

Reference	Maternal clinical history	No. of pregnancies	Pregnancy 1	Pregnancy 2	Pregnancy 3	Pregnancy 4	Pregnancies 5 & 6	Pregnancy 7
Vincent et al. (95) Brueton et al. (00)	Completely asymptomatic throughout Anti-AChR found after sixth pregnancy	6	MA: 24 yr nasal speech, myopathic facies, conductive + sensorineural hearing loss	MA: nr Reduced fetal movement, IUGR, AMC, micrognathia Stillbirth at 36 wk PM: lung hypoplasia	MA: nr AMC on ultrasound, TOP at 19 wk PM: lung hypoplasia, scoliosis, CNS abnormalities	MA: nr AMC + micrognathia on ultrasound at 17 wk, TOP PM: as before	MA: nr (5) AMC + micrognathia on ultrasound at 17 wk, TOP PM: as before (6) AMC on ultrasound at 15-16 wk, TOP PM: as before	MA: nr Anticholinesterase therapy Plasma exchange from 10 wk AMC on ultrasound at 19 weeks, TOP

AMC, arthrogryposis multiplex congenita; AChR, acetylcholine receptor; IUGR, intrauterine growth retardation; nr, not reported; MA, maternal age; PM, postmortem; TOP, termination of pregnancy.

requested anti-AChR antibody levels in the totally asymptomatic mother. In three other instances, in which the number of siblings was greater than three, all or all but the first pregnancies were affected (Moutard-Codou et al., '87; Barnes et al., '95; Vincent et al., '95), and this was probably also the case in some of the smaller sibships reported (Tables 1–4). The severity of the clinical spectrum did not correlate with the birth order.

#### Disease status of the mother

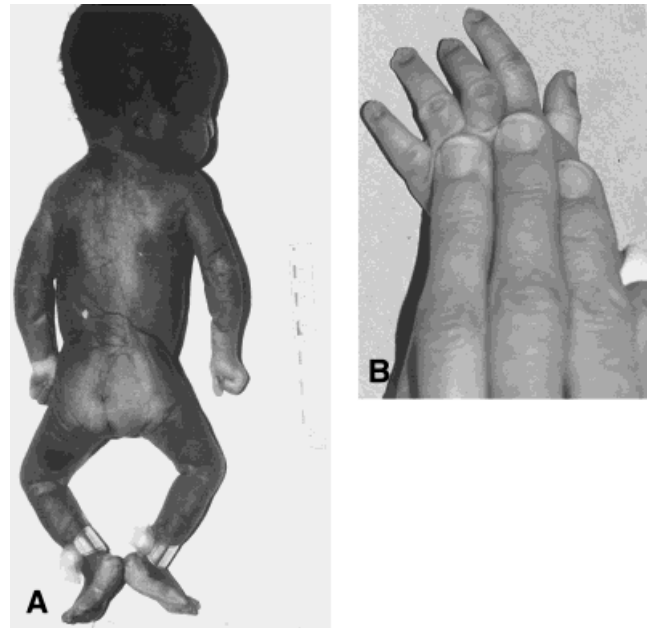
The onset of MG in the mother, when MG was present, was almost exclusively confined to adolescence. There was no obvious correlation between maternal disease severity and AMC, and there are a number of cases in which the diagnosis of MG was not made until during the pregnancy or after the birth of the affected baby (Holmes et al., '80; Dulitzky et al., '87; Moutard-Codou et al., '87; Barnes et al., '95; Vincent et al., '95). Indeed, as mentioned above, in the case reported by Vincent et al. ('95), no symptoms or signs of MG were found at any time.

#### Response to treatment of maternal MG

One important reason for recognising this condition is that it is potentially treatable. In the family reported by Carr et al. ('91), treatment with anticholinesterases and thymectomy did not influence the outcome of pregnancy, but extensive plasma exchange (six sessions at 15–17 weeks gestation) followed by prednisolone (80 mg every other day) was associated with improvement in a subsequent pregnancy. After treatment with pyridostigmine and thymectomy, the patient reported by Holmes et al. ('80) had a baby born with only fifth finger contractures (L.B. Holmes, personal communication). A similar outcome was obtained after thymectomy and treatment with prednisolone and azathioprine for the patient reported by Barnes et al. ('95) (Fig. 1). Another successfully treated case was given intravenous IgG and plasma exchange during pregnancy (Newsom-Davis, '98; unpublished observations). For the asymptomatic woman with six affected pregnancies (Table 4), repeated plasma exchange from 10 weeks onward prolonged the period of fetal movements for 3 weeks (Vincent et al., '95; Brueton et al., '00), but unfortunately AMC subsequently developed.

#### AChR and antibodies in typical MG patients

The AChR is an oligomeric membrane protein which, in normal adult muscle, is made up of five subunits:  $\alpha$ ,  $\gamma$ ,  $\beta$ ,  $\epsilon$ , and  $\delta$ . It is essential for the transmission of impulses from nerve to muscle and exists in two isoforms that differ by one subunit; during early development (and after denervation), a  $\gamma$ -subunit is present instead of the  $\epsilon$ -subunit. In typical MG, a high proportion of the antibodies bind to an epitope on the  $\alpha$ -subunits, called the main immunogenic region (Tzartos et al., '80). However, many patients also have antibodies specific for the fetal isoform of the AChR (Newsom-Davis et al., '87), probably binding to the  $\gamma$ -subunit.



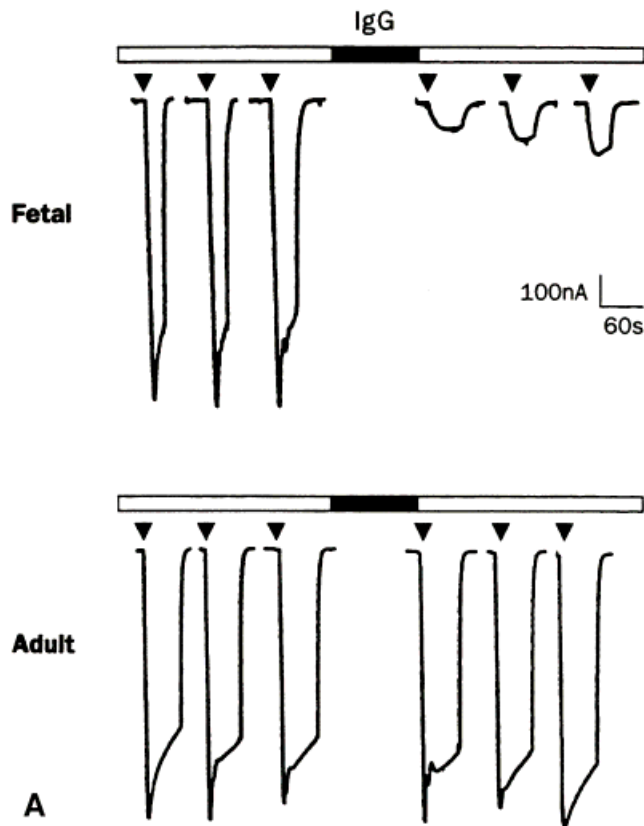
**Fig. 1.** Children born pre- and posttreatment to mother reported by Barnes et al. ('95). **A:** Postmortem picture of fourth child showing arthrogyriposis multiplex congenita (AMC). **B:** Mild finger contractures and mild lung hypoplasia were the only problems in her sixth pregnancy after treatment.

Antibodies in MG act by three mechanisms: complement-mediated damage of the muscle membrane, antibody-induced reduction of AChR numbers, and direct block of AChR function (Drachman '94). In most MG patients, the latter is not thought to be an important pathogenetic mechanism. There is some evidence that women whose babies suffer from neonatal MG, have higher titres of antibodies and a higher proportion that bind to epitopes on the  $\gamma$ -subunit (Vernet der Garabidien et al., '94) but, in most respects, it is unclear as to why only a few babies develop neonatal MG. It may be that the neonatal neuromuscular junction is relatively resistant to the effect of antibodies, perhaps due to its immaturity and higher turnover of AChR, and there may be less complement-mediated damage.

#### Antibodies that block the function of fetal AChR in mothers of AMC babies

Our interest in this area was stimulated by the severity of the recurrent AMC in babies of MG mothers (Barnes et al., '95). We have now studied sera from seven women with AMC babies, and the results are remarkably similar.

IgG antibodies in serum of mothers with AMC in their babies inhibit selectively the function of the fetal form of the AChR which expresses the  $\gamma$ -subunit, but have no effect on function of the adult form, that expresses the  $\epsilon$ -subunit (Vincent et al., '95; Riemersma et al., '96) (Fig. 2A). The two forms differ by one subunit (see above). In one case, similar effects were found with serum from an affected fetus at 18



**Fig. 2.** Effects of maternal immunoglobulin G (IgG) on fetal and adult acetylcholine receptor (AChR) function. **A:** Effect on human adult and fetal AChR in vitro. *Xenopus* oocytes were first injected with cDNA for the human AChR subunits in order to induce their expression. Whole-cell currents were measured in oocytes expressing fetal (upper) or adult (lower) human AChR. The currents were activated by 30–60-sec additions of 1  $\mu\text{mol/L}$  acetylcholine to the bath (arrow) every 10 min (traces not continuous). At the solid bar, the bathing solution was exchanged for one containing maternal IgG (1:50 dilution) for 40 min. Subsequent additions of ACh induced normal-size currents with adult AChR, but markedly reduced currents with fetal AChR (Reprinted



with permission from Vincent et al., '95.) **B:** Effects of exposure to maternal IgG on mice in utero. Pregnant mice were injected daily, from E11–E17, with plasma from multiparous women with healthy babies or from women with arthrogyriposis multiplex congenita (AMC) babies. The control treated fetus (left) and AMC-treated fetus (right) were removed under terminal anaesthesia at E18 and fixed in 95% ethanol. The control fetus is normal in appearance. The AMC fetus shows torticollis and asymmetry of the shoulders, the left forelimb is internally rotated and abducted, and scoliosis of the spine is also present. (Reprinted with permission of the Rockefeller University Press from Jacobson et al., '99.)

weeks gestation (Vincent et al., '95). Surprisingly, in the study conducted by Vernet-der Garabedian et al. ('94), the three mothers whose babies were severely affected by arthrogyriposis and hypotonia did not have particularly high titres of antibodies directed against fetal AChR by immunoprecipitation assays. However, these sera were shown subsequently to inhibit dramatically the function of fetal AChR and to have little or no effect on adult AChR (Riemersma et al., '96). Thus, these studies strongly suggest that there is a population of anti-AChR antibodies, mainly directed against a functional determinant specific to fetal AChR, that are responsible for causing fetal paralysis leading to AMC. The reason that these particular antibodies were not detected in the routine immunoprecipitation assay used by Vernet-der Garabedian et al, is that the fetal specific, functional site is occupied by  $^{125}\text{I}$ - $\alpha$ -bungarotoxin.

#### Placental transfer model of antibody-mediated AMC

It is well established that, for normal development, the fetus needs to be able to move freely at 7–8 weeks gestation onward. Maternal IgG begins to cross the placenta substantially at 14–16 weeks gestation onward, and fetal AChR is not detected in the fetus after 33 weeks. Thus, antibodies interfering with fetal AChR function will be at their most pathogenic at 14–33 weeks gestation. In several cases of AMC with maternal anti-AChR antibodies, lack of fetal movement and developing AMC have been noted in the middle trimester and the pregnancies terminated.

We have established an experimental model to look at the effects of maternal antibodies on fetal development. Some degree of placental transfer of human antibodies across the mouse placenta was demonstrated using sera from women affected by systemic lupus er-

ythematosis (SLE) (Guzman-Enriquez et al., '90). In quantitative studies, we found that human antibodies can be efficiently transported to the mouse fetus (probably via the yolk sac rather than the placenta). MG serum was injected by the intraperitoneal route into pregnant mice from E10–E17, producing high levels of anti-AChR in the fetuses, equivalent to levels in the mouse dams; most of the transfer occurred after E15. Injection of plasma from the mothers reported by Barnes et al. ('95) and Vincent et al. ('95) produced striking evidence in favour of the role of antibodies in causing this condition: none of the mice delivered healthy pups, and there were no survivors among the offspring (although the mouse dams themselves were unaffected). Moreover, when fetuses were removed earlier under terminal anaesthesia, many pups showed multiple contractures, craniofacial dysmorphisms, cutaneous oedema, kyphosis/scoliosis, multiple pterygia, low-set ears, and hypotonia—all abnormalities associated with AMC (Fig. 2B). On further morphological examination, hypoplastic lungs and cerebellar atrophy were seen in a few fetuses. Control serum/plasma injected mice gave birth to normal pups that thrived. Studies on plasma from other AMC mothers are in progress.

In spite of the convincing evidence in favour of antibodies to fetal AChR as the major cause for AMC in MG mothers, or in those with anti-AChR without MG, there are some interesting additional features that complicate the interpretation. Postmortem examination of the reported human cases revealed (Tables 1–4) not only features that might be consistent with fetal paralysis, but also involvement of other organs such as cerebrum, cerebellum, and heart. One possibility is that the plasma IgG from these mothers also reacts with other fetal antigens and causes systemic anomalies unrelated to lack of fetal movement. Some evidence in favour of this comes from the high incidence of unrelated abnormalities in the fetuses of mice injected with AMC or MG plasmas, particularly atrioseptal defect in one and a possible Chiari malformation in another (Jacobson et al., '99). It is possible that during development of the human (or mouse) fetus, the blood-brain barrier is sufficiently leaky to allow IgG antibodies to gain access to the central nervous system and cause damage that would not be seen in a normal adult.

## DISCUSSION

Maternal MG is a rare, but significant, cause of congenital contractures in newborns. As a few mothers in some of the reported cases had not been diagnosed previously as having MG and, in one case remained asymptomatic, we suggest that maternal AChR antibodies should be measured in all cases of AMC of unknown cause. This test is routinely available for the diagnosis of MG.

The high recurrence risk (100% in many cases), much greater than would be predicted for a genetic disorder, has important implications for the counselling of these mothers. Particularly as treatment, at

least in some cases, seems to have been effective in preventing further affected children.

The role of maternal antibodies is suggested by normal development and movement early in pregnancy, with subsequent lack of movement and joint contractures, and is confirmed by the presence of anti-AChR antibodies particularly directed at fetal AChR. However, it is possible that some other cases of AMC are caused by antibodies to different neuronal or muscle antigens; for instance, antibodies interfering with nerve conduction or muscle contraction could give rise to a similar phenotype. Further experimental studies are needed to test this possibility.

The establishment of an animal model of transfer of the pathogenic antibodies will not only help to elucidate the mechanisms involved in inducing fetal abnormalities, but may permit testing of experimental treatment protocols as well. It may be possible to block placental transfer of IgG during the most critical phase of intrauterine life.

One intriguing question that arises is the stimulus that results in production of antibodies that are so strongly fetal specific. It is possible that maternal sensitisation follows exposure to fetal antigens during or after the first pregnancy, or perhaps in a previous pregnancy that was spontaneously aborted. Alternatively, defects in expression of fetal AChR on muscle-like cells in the thymus could lead to lack of immune tolerance. There may be genetic factors that make these mothers more likely to make antibodies to fetal AChR. Future studies will look at the natural history of these antibodies in asymptomatic mothers, and at their prevalence in other MG patient groups, including parous and nonparous individuals.

We conclude with a more general hypothesis—that immune mechanisms could be the cause of congenital abnormalities other than AMC. Since maternal antibodies to fetal receptors are not always associated with maternal disease, one cannot exclude the possibility that quite different congenital disorders are caused by antibodies to fetal-specific antigens or to those antigens that are only accessible during intrauterine life. Our animal model provides a way in which this hypothesis can be tested.

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