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## TRANSIENT NEONATAL AUTOIMMUNE AUTONOMIC GANGLIONOPATHY

### OPEN

Autoimmune autonomic ganglionopathy (AAG) is an acquired reversible neuroimmunologic disorder of autonomic ganglia in the sympathetic, parasympathetic, and enteric nervous systems. Antibodies specific for ganglionic nicotinic acetylcholine receptors (gAChRs) impair fast synaptic transmission between preganglionic and postganglionic neurons.<sup>1</sup>

Clinical manifestations of AAG reflect peripheral autonomic nervous system dysfunction. Attenuated sympathetic ganglionic transmission produces orthostatic hypotension, low serum catecholamines, and hypohydrosis/anhydrosis.<sup>1–3</sup> Parasympathetic ganglionopathy causes sicca, gastrointestinal inertia, atonic bladder, tonic pupils, and blunted cardioacceleration.<sup>1–3</sup> These pandysautonomic symptoms are typically subacute, evolving over days to weeks.<sup>2</sup> Spontaneous improvement may occur but is usually incomplete. Immunomodulatory therapy is often effective, even for chronic symptoms.<sup>3</sup>

Transmission of maternal antibodies across the placenta has been described in myasthenia gravis (MG) and systemic lupus erythematosus.<sup>4</sup> Transient and self-limited neonatal symptoms, similar to the maternal disorder, inculcate the antibody as pathogenic and serve as a natural passive transfer experiment. This report describes a case of transient neonatal AAG, further supporting the pathogenicity of gAChR antibodies.

**Case report.** A 36-year-old mother with seropositive AAG (gAChR antibody 1.33 nmol/L at 21 months before delivery, normal <0.05) initially had orthostatic hypotension and bowel dysmotility that improved with immunoglobulin (Ig) therapy. IVIg treatments were discontinued at the beginning of gestation secondary to mild allergic reactions and significant postinfusion malaise. Serial nonstress tests beginning at gestational week 26 were within normal limits. Birth weight at term delivery was 2,208 g, with 1-minute and 5-minute Apgar scores of 8. Maternal and fetal cord blood was simultaneously collected. Serum testing for gAChR antibodies was performed, as previously described by a radioimmunoprecipitation

assay involving <sup>125</sup>I-epibatidine-complexed acetylcholine receptors from human neuroblastoma cells (IMR-32).<sup>1</sup> Puerperal maternal and fetal gAChR antibody levels were 0.31 and 0.36 nmol/L, respectively.

The baby presented with constipation, abdominal bloating, and delayed meconium passage, with his first bowel movement occurring past 48 hours. His 2 older siblings shared similar symptoms and were born when the mother was symptomatic yet undiagnosed. At day 20, physical examination revealed a normal tear meniscus with reactive pupils and unremarkable dermatologic screening. A 15-minute hanging orthostatic challenge test was conducted via axillary suspension. Using a neonatal brachial cuff, supine blood pressure (BP) measured 98/59 mm Hg (mean arterial pressure [MAP] 70 mm Hg) and dropped to 71/36 mm Hg (MAP 47 mm Hg). By day 20, serial gAChR antibody levels declined to 0.10 nmol/L and were undetectable by day 90, at which point bowel function had normalized.

**Discussion.** This case supports the pathogenicity of gAChR antibodies and represents an *in vivo* natural passive transfer experiment. The isolated finding of transplacental passage of gAChR antibodies cannot be considered definitive with regards to pathophysiologic cause and effect, especially as symptoms were limited to gastrointestinal deficits and modest orthostasis. However, experimental AAG induction in animal models<sup>1</sup> via both inoculation and passive transfer increases the significance of the current findings. Additional evidence supports a pathogenic role for the passively transferred antibodies. For example, similar to the passive transfer model of AAG, the duration of symptoms correlated to the presence of the antibody (i.e., ~21 days). The half-life of the passive antibody is comparable to the timeline for anti-nACh receptor antibody neonatal MG.<sup>4</sup>

The relatively restricted clinical manifestations are consistent with previous reports of patients with AAG with lower antibody levels.<sup>2</sup> In adults, isolated gastrointestinal dysmotility predominated at low antibody levels (0.05–0.20 nmol/L), whereas pupillomotor and urinary dysfunction appeared at higher levels (>0.50 nmol/L).<sup>1</sup> Severe orthostasis (maximal fall in systolic BP ~100 mm Hg) and diffuse pandysautonomia are associated with anti-gAChR levels above 1.0 nmol/L.<sup>2</sup>

Gastrointestinal dysmotility is a very frequent manifestation of AAG; thus, gAChR antibodies should be screened in the absence of other obvious causes, such as Hirschsprung disease and anorectal abnormalities. Neonates may have greater vulnerability to gastrointestinal manifestations due to postnatal changes in morphologic and electrophysiologic properties in enteric neurons.<sup>5</sup> While enteric neurons respond to nicotinic agonists and exhibit Ca<sup>2+</sup> transients during early embryogenesis, these neurons only become capable of coordinating gut motility in the perinatal period.<sup>5</sup> Neuroenteric immaturity may increase susceptibility to maternal gAChR antibodies. Finally, neurotransmitter blockade during development may slow migration of enteric neural crest cells through the gastrointestinal tract.<sup>6</sup>

Although AAG is a rare disorder, increasing recognition will translate to improved supportive treatment and bowel care protocols. Recognizing that only 10%–15% of infants born to mothers with MG develop neonatal MG,<sup>4</sup> there may be a role for subspeciating IgG class, as IgG1 preferentially undergoes transplacental flux.<sup>7</sup> Whether maternal antibody-depleting therapies result in lower fetal levels or milder phenotypes is unknown. Autonomic monitoring should therefore be considered in infants of mothers with AAG.

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