ANTI-MUSK ANTIBODY AFTER THYMECTOMY IN A PREVIOUSLY SEROPOSITIVE MYASTHENIC CHILD

We report a young girl with myasthenia gravis (MG) who was first seen at age 2 for unexplained falls, diplopia, and ptosis. The patient was born as a full-term spontaneous vaginal delivery and spoke her first words and started walking at the age 10 months. The child was physically active initially and loved to play and run. At age 27 months, the patient started having difficulty rising up while she was lying or sitting. She also experienced increasing difficulty swallowing without any dyspnea.

Diagnostic workup at age 2 revealed a positive neostigmine test with improved muscle strength. Electromyography showed a decrement of 20 to 28% with 3- and 10-Hz repetitive stimulation in two nerve muscle pairs; anti-acetylcholine receptor antibody (anti-AChR Ab) levels were 0.6 and 1.3 on consecutive testing (N 0 to 0.4). Chest radiograph and CT scan did not reveal any additional findings. Laboratory analysis including thyroid profile and metabolic and hematologic panels was unremarkable.

The young girl’s mother had a history of Hashimoto thyroiditis. Her paternal grand mother had primary biliary cirrhosis, and her paternal aunt had a mixed connective tissue disorder.

The patient was started on treatment with pyridostigmine (7 mg/kg/day) in divided doses with minimal response. Her family elected to use IV immunoglobulin (IVIG), given a choice between plasmapheresis and IVIG. The patient did demonstrate better response to IVIG (2 g/kg) and subsequent low-dose methylprednisolone compared with the initial regimen with improvement in weakness. Thymectomy was advised at an earlier age because of her overall poor response to other treatment modalities. Following surgery the patient’s weakness and balance problems gradually improved and anti-AChR Ab became negative. Steroid requirements were decreased, and the patient lost her cushingoid appearance and improved furrowing of tongue, which was initially observed. Her symptoms were relatively controlled subsequently for another 18 months.

At age 57 months, the patient began experiencing exacerbations of weakness. Detailed laboratory workup revealed the presence of anti-MuSK Ab and the absence of anti-AChR Ab. The patient was subsequently started on IVIG; later, low-dose methylprednisolone was added, to which patient showed improved response. Currently the patient is 7 years old and continues to respond well to the immune modulation therapy.

Discussion. Circulating antibodies to the AChR are found in up to 80% of patients with autoimmune MG. Conventionally patients who do not test positive for anti-AChR Ab are considered seronegative MG (SNMG). Anti-MuSK Ab have been described in about 40 to 50% of the latter group.1-3 Lately the term “SNMG” is being reserved for patients who test negative for all antibodies. Most of the reported cases of anti-MuSK MG had onset of weakness later in life. The disease presentation in anti-MuSK MG predominantly involves facial and bulbar muscles, but other distinct clinical presentations have been described.1-6 Response to treatment in anti-MuSK MG was found to be not typical of MG, with poor response to anticholinesterase inhibitors and variable response to immunosuppressive therapy. Improvement after plasma exchange was consistently dramatic, and none who underwent thymectomy had apparent benefit from surgery.5,6 Most patients will be placed on steroids or other immunosuppressive agents.5 We are aware of one reported childhood case of MG with predominant facial bulbar symptoms with a longitudinal fluctuating clinical course and delayed adult-onset appearance of anti-MuSK Ab with overall better response to plasma exchange therapy. It was not clear whether the patient was anti-AChR Ab positive at any time.7

Our reported case had fluctuating pattern of weakness longitudinally over the years with clinical improvement and anti-AChR Ab becoming negative subsequently, which is an unusual clini-
A JAPANESE ADULT FORM OF CPT II DEFICIENCY ASSOCIATED WITH A HOMOZYGOUS F383Y MUTATION

Carnitine palmitoyltransferase II (CPT II) deficiency is an inherited autosomal-recessive disorder of the fatty acid metabolism. CPT II deficiency has three phenotypes: a lethal neonatal form, an infantile form, and an adult form. The adult form of CPT II deficiency, which is characterized by recurrent episodes of muscle pain and rhabdomyolysis, is the most common disorder of the fatty acid metabolism affecting skeletal muscles. We describe a Japanese adult form of CPT II deficiency with a homozygous F383Y mutation.

Case report. The patient was a 21-year-old woman born of nonconsanguineous parents. Her brother had died as an infant, and Reye syndrome was suspected based on his liver biopsy. Her sister also died as an infant.

At age 2 years, she had a hypoglycemic episode (blood sugar 9 mg/dL). When she caught a cold at age 19 years, myalgia of the right upper limb appeared and progressed rapidly to other muscles. The laboratory data showed a massively increased creatine kinase (CK) level (101,790 IU/L). Her blood urea nitrogen (BUN) was normal (19.7 mg/dL), whereas the creatinine (CREA) had increased (3.84 mg/dL). Her urine was dark colored, but no ketonuria was observed. At age 21 years, she experienced myalgia of the bilateral thighs after flu-like symptoms. The maximal CK was 62,520 IU/L, the BUN was 7.7 mg/dL, and the CREA was 0.56 mg/dL. However, no ketonuria was observed. After these episodes, she was admitted to our hospital.

She was 167 cm tall and weighed 80 kg. She had no muscle symptoms. The laboratory data showed no abnormalities. The chest roentgenogram, electrocardiography, and echocardiography findings were also normal. No significant change in the blood lactate and pyruvate levels was found in the ischemic forearm exercise or ergometer exercise tests.

We tentatively diagnosed a disorder of the fatty acid metabolism. The serum total carnitine (14.4 μmol/L, reference 45 to 91) and free carnitine (7.2 μmol/L, reference 36 to 74) had decreased, whereas the acylcarnitine (AC) was normal (7.2 μmol/L, reference 6 to 23). The AC/free carnitine ratio was elevated (1.0, reference < 0.4). The serum AC analysis by tandem mass spectrometry showed a markedly increased ratio of (C16:0-AC + C18:1-AC)/C2-AC (1.16, reference < 0.048). A muscle biopsy specimen from the right quadriceps revealed no significant
Eight pairs of PCR primers were designed by overlapping to cover the complete stretch of the coding sequence. Each PCR-amplified gene product was subjected to DNA sequencing on an automated DNA sequencer using the PCR primer as the sequencing primer and the BigDye Terminator v3.1 cycle-sequencing kit. The sequences from the 5’ end were confirmed by those from the 3’ end. The eight DNA sequences obtained from eight PCR products were assembled, and the resulting coding sequence was analyzed.6

Figure Direct DNA sequencing of the carnitine palmitoyltransferase II–specific PCR products

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<th>Codon 383</th>
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<tr>
<td>Ala</td>
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Discussion. We diagnosed an adult form of CPT II deficiency in this patient because of her recurrent rhabdomyolysis episodes. The relationship between the CPT II activity level and the phenotype is understood to a certain extent. In previous reports, the CPT II activity in fibroblasts ranged from 15% to 26% of normal controls in the adult form and from 4% to 10% in the infantile form.7 In our case, the residual CPT II activities ranged from 2% to 7% of normal controls. These results are more similar to the infantile form than the adult form. Previous reports on genotype–phenotype correlations have shown that the S113L mutation is common in the adult form and the F383Y mutation is related to the infantile form. Since a Japanese infantile form with an F383Y mutation has been reported, three cases with same mutation have been reported, two from Japan and the other from France.2,3 Two cases had a heterozygous mutation, and the other was a Japanese infantile form with a homozygous F383Y mutation. All previous cases were the infantile form. Our patient is the first case of an adult form and the second case of a homozygous F383Y mutation. These results suggest that the F383Y mutation is not specific to the infantile form and seems to be more common among Japanese than among Caucasians. In addition, this patient’s siblings may possibly have an infantile form. We think that the phenotype depends not only on the genotype and the CPT II activity but also on other unknown factors.

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TOXOCARIASIS OF THE CNS SIMULATING ACUTE DISSEMINATED ENCEPHALOMYELITIS

Toxocariasis is the infection of the human host with either *Toxocara canis* or *Toxocara catis*. Their definitive hosts are the domestic dog and cat, in which they live as adults within the lumen of the small intestine. Humans become infected after ingesting embryonated eggs from soil (geophagia, pica) or after exposure to dirty hands, raw vegetables, or larvae from undercooked giblets.

The dominant clinical manifestations associated with toxocariasis are classified according to the organs affected. There are two main syndromes: visceral larvae migrans (VLM), which encompasses diseases associated with the major organs; and ocular larva migrans, in which pathologic effects on the host are restricted to the eye and the optic nerve. Clinical involvement of the CNS due to *Toxocara* species is rare and probably occurs as a result of hematogenous dissemination.

This report describes a 2-year-old girl presenting neurotoxocariasis and an MRI pattern similar to acute disseminated encephalomyelitis (ADEM).

Case report. A 2-year-old girl presented monthly episodes of fever and cough for approximately 1 year. Treatment during these episodes was based on antibiotics. The girl lived with her grandparents in a modest home where she used to play on the ground with a female dog, but there was no other positive epidemiologic information.

A month before her hospital admission, she entered a new cycle of fever and cough, but this time without improvement despite the use of amoxicillin and cephalaxin. On the 20th day of fever, she was vomiting and had diarrhea. Four days later, she presented difficulty in walking and sitting, dysarthria, and nystagmus. Neurologic examination revealed ataxic gait, lower limb hyperreflexia with bilateral Babinski sign, nuchal rigidity, and Brudzinski sign.

Complete blood count showed leukocytosis of $15.3 \times 10^3\mu$L (34% neutrophils, 52% lymphocytes, 8% atypical lymphocytes, and 6% monocytes). CSF analysis showed pleocytosis of 277/\muL (9% neutrophils, 11% eosinophils, 68% lymphocytes, and 12% monocytes), glucose of 61 mg/dL, and protein of 67 mg/dL.

Magnetic resonance (MR) images were similar to those from ADEM (figure A and B), and a few days later, results from blood and CSF demonstrated positive antibodies against *Toxocara canis* (immunoglobulin G [IgG]-ELISA and IgG4-ELISA). Serum samples were diluted to 1:100 before use, with a cutoff value (COV) of 0.144. CSF samples were diluted to 1:10 before use, with a COV of 0.199. The results of serum and CSF, expressed in optic density, were 0.530 and 0.304, respectively.

Treatment was started with prednisolone (2 mg/kg/day) for 15 days and thiabendazole (50 mg/kg/day) for 30 days. In 2 months, MR images and neurologic examination results were completely normal (figure C and D).

Discussion. In 1951, Beautyman and Woolf published a report of a child with clinical and pathologic evidence of neurologic involvement due to an encapsulated larva, identified as probably *Ascaris lumbricoides*. In 1956, Nichols provided more precise data on the morphology of *Toxocara*, and in 1966, Beautyman and others suggested that the parasite described was not *A. lumbricoides*, but *T. canis*. This study was the first report of a case of CNS toxocariasis.

The diagnosis of neurotoxocariasis is based on several findings: high serum titers of *T. canis* antibodies (measured with sensitive immunologic methods, ELISA or Western blotting, that use *Toxocara* excretory–secretory antigens), eosinophilia in the blood or CSF, the demonstration of an intrathecal synthesis of anti–*T. canis* antibodies, and close contact with dogs. The clinical and
radiologic improvement, as well as the normalization of the CSF parameters during antihelminthic therapy, supports the diagnosis.2

Clinical CNS disease is related to the number of larvae entering the brain and to the severity of damage and inflammation.4 The clinical spectrum of neurotoxocariasis is broad, causing various syndromes: eosinophilic meningoencephalitis, encephalitis, extramedullary space–occupying lesion, brain vasculitis, seizures, and probably behavior disorder.5

Our patient fulfilled clinical, laboratory, and epidemiologic criteria for the diagnosis of CNS toxocariasis. Improvement after the institution of specific treatment for toxocariasis corroborated the diagnosis. Interestingly, our patient presented image findings on MRI that were initially interpreted as ADEM. Reports of several MRI alterations due to Toxocara infection of the CNS include vasculitic areas, focal lesions, and nonspecific T2-weighted areas of increased signal corresponding to granulomas, microhemorrhages, and cortical necrosis due to infarction.3,5 No descriptive articles on ADEM pattern images from MRI after CNS toxocariasis infection have been reported yet.

Infection due to Toxocara canis must be considered in the differential diagnosis of eosinophilic meningoencephalitis or meningitis. This report of MR images compatible to ADEM should remind us to search also for neurohelminthiasis when faced with this pattern of images.

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