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Clinical/Scientific Notes

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STIFF EYES IN STIFF-PERSON SYNDROME

The clinical findings of stiff-person syndrome (SPS) include trunk and limb muscle stiffness and paroxysmal cramps. Antibodies directed against glutamic acid decarboxylase (GAD) has been associated with SPS. We report a patient with SPS and anti-GAD antibodies (antiGAD-Abs) with a prominent supranuclear gaze palsy and bradykinesia mimicking progressive supranuclear palsy (PSP).

Case report. A 45-year-old former fighter pilot presented with an 18-month history of stiffness and gait problems that began with several falls backwards while training for a marathon. Six months later, she noted stiffness of the left arm and leg. She reported painful back and limb spasms when startled by touch. Her history was notable for pernicious anemia.

Examination (video) including head thrust revealed a supranuclear vertical gaze palsy and vertical greater than horizontal saccade hypometria with prolonged saccade latency. Vertical pursuits were saccadic, but horizontal pursuits were normal. Convergence was impaired. She had a mildly masked facies, asymmetrically increased axial and limb tone, bradykinetic gait and limb movements, and no arm swing while walking. The remainder of the examination was unremarkable.

Brain and spinal cord MRI scans showed mild cortical atrophy. EMG showed continuous motor activity at rest, normal 3-Hz repetitive stimulation, and a mild sensory neuropathy. CT of the chest, abdomen, and pelvis were normal. An extensive evaluation including paraneoplastic, amphiphysin, antigliadin, and intrinsic factor antibodies, rheumatologic markers, hemoglobin A1c, and fasting glucose were normal. Serum antiGAD-Abs were abnormally elevated at 71.6 U/mL (<1.45 U/mL). During the course of the next year, serum antiGAD-Abs were measured several times and were markedly elevated on all occasions. CSF analysis was acellular with protein of 48 mg/dL (<45 mg/dL), and antiGAD-Abs were absent.

Videonystagmography (Synapsys Ulmer VNG C4-12.2, image frequency 30/s) initially revealed normal saccade latencies to horizontal and vertical targets, lengthening with repetition to exceed 7 s. Saccades were hypometric, and slowed after 180 s of horizontal testing (figure, A) and 370 s of vertical testing (figure, B). Horizontal pursuit at 0.3 Hz showed range restriction with normal gains, fatiguing to cessation after 30 s (figure, C). Fatigue also became evident after 40 s of normal gain during optokinetic and vestibuloocular reflex testing, with loss of further responses. Caloric and head thrust responses were preserved and no pathologic nystagmus was seen.

Treatment with monthly IV immunoglobulin (IVIg) was initiated and the patient experienced prompt improvement of her bradykinesia and rigidity. The patient chose to participate in a placebo-controlled SPS treatment trial at another institution, and during this time her symptoms progressed significantly. She became wheelchair bound due to profound rigidity and bradykinesia. She developed severe horizontal and vertical supranuclear gaze ophthalmoparesis, dysphagia, incontinence, and a violent head, trunk, and arm tremor over the following 12 months. After resumption of monthly IVIg treatment for 4 months, there was significant improvement in ophthalmoparesis, tremor, and ability to ambulate, but extremity stiffness remained.

Discussion. Few previous reports have focused on abnormalities of eye movements in SPS.[1-4] AntiGAD-Abs have been associated with cerebellar limb dysfunction and different types of nystagmus with[2,4] and without[5] SPS. Others have noted SPS, nystagmus, and abduction deficits in the absence[2] and presence of myasthenia and thymoma.[3] Slowed and impaired saccade initiation has also been described[1,3,5] but not in this fatiguing pattern. Our patient had parkinsonism rather than ataxia, no anti-acetylcholine receptor antibodies, and repetitive nerve stimulation and CT chest studies were unremarkable. The most salient clinical findings that suggested a diagnosis other than PSP in this patient were delayed saccade initiation with repetitive saccades, spasms induced by startle, and prominent early upgaze palsy. Unlike the findings in our patient, PSP is usually characterized by decreased saccade velocity and accuracy, square-wave jerks, preserved saccade latency, and a prominent downgaze palsy, although

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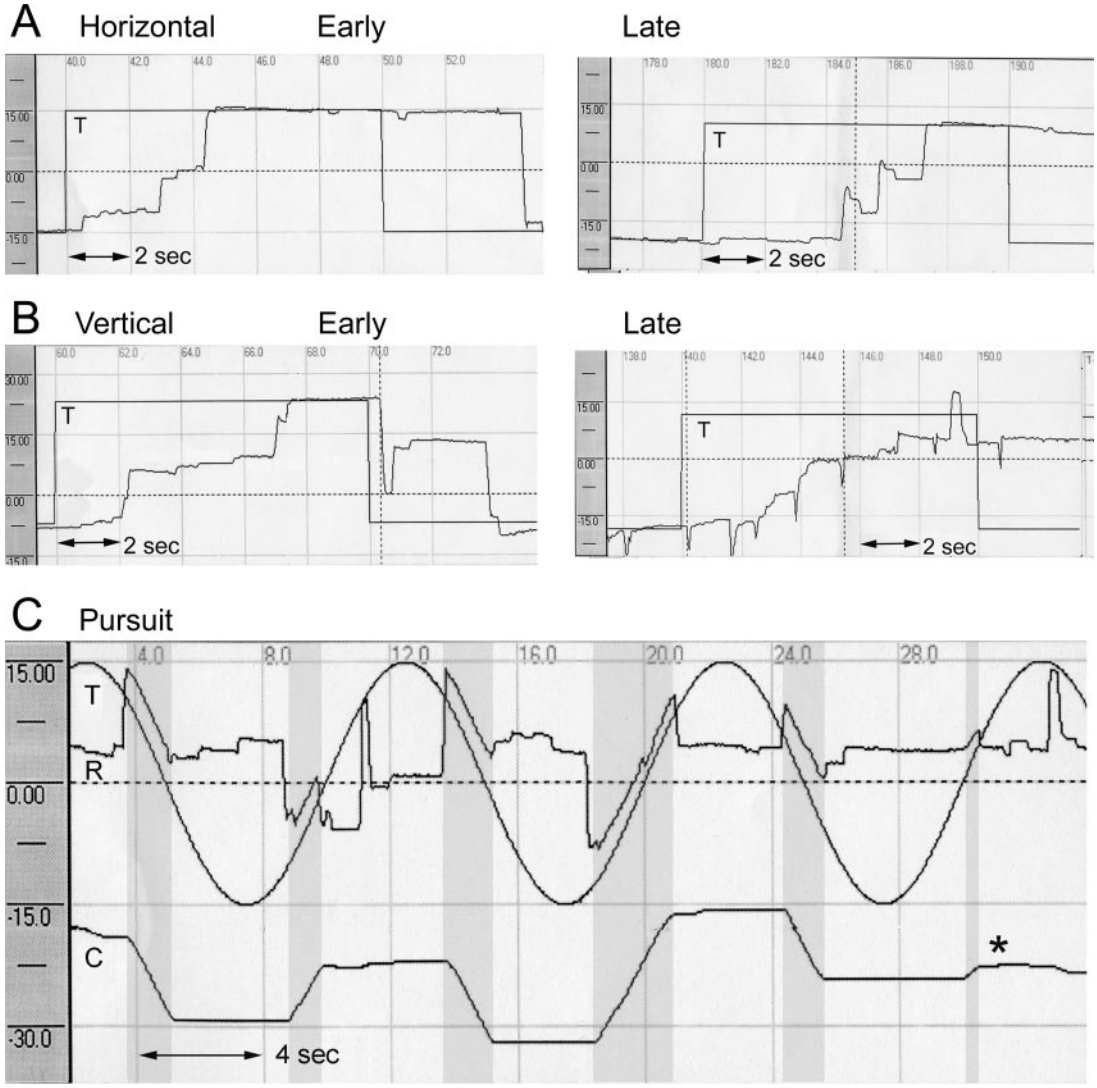
Figure Videonystagmography of horizontal and vertical saccades and pursuit



(A) Horizontal saccades. Early VNG tracing shows R hypometria, latency = 500 msec; L normal accuracy, latency prolonged > 4 s; Late tracing 144 s later shows R latency >4 s, velocity slowed to 57 °/s (15° saccade). (B) Vertical saccades. Early tracing shows hypometria with upward latency >2 s, downward latency normal. Late tracing recorded 310 s later shows slowing, downward latency >6 s, and worsening hypometria. (C) Horizontal smooth pursuit. Shaded bars show accurate tracking within a narrow range, cut off before the target endpoints are reached. *Cessation of all pursuit after 30 s of recording. T = target, R = raw data, C = cumulative tracing with saccades removed.

upgaze and downgaze may be equally affected in some cohorts of PSP.[6] The VNG finding of progressively delayed saccade latency in our patient is unique.

While we cannot with certainty explain the pathophysiology behind these findings there could possibly be a connection to neurons termed "fixation cells" at the level of rostral superior colliculus which inhibit the generation of saccadic eye movements. Inhibition of these cells with a GABA antagonist in monkeys results in increased saccade latency while GABA agonists reduce saccade latency.[7] The identification of the antiGAD-Abs enabled the patient to be effectively treated with immunomodulation. This observation adds a treatable condition to the differential diagnosis of PSP.

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ENZYME REPLACEMENT THERAPY FOR INFANTILE-ONSET POMPE DISEASE: CURSE OR CURE?

Pompe disease is a rare progressive autosomal recessive disorder caused by a deficiency of lysosomal hydrolase acid α-glucosidase.[1] This results in accumulation of glycogen in the lysosomes of all tissues, particularly cardiac and skeletal muscle. Historically, infantile-onset Pompe presents with cardiomegaly, hepatomegaly, weakness, and hypotonia leading to death due to cardiorespiratory failure in the first year of life.[2]

The efficacy for specific enzyme replacement therapy (ERT) for Pompe disease has recently been reported in a cohort of infant onset Pompe patients. Eighteen children under the age of 6 months were given ERT and all survived. However, none were ventilated; ventilator dependency was an exclusion criterion for the study.[3] We report two cases of infantile Pompe disease requiring mechanical ventilation while receiving ERT.

Case 1. A 3-month-old boy was referred with cardiorespiratory failure. At 4 weeks a systolic murmur was heard, and cardiomegaly on X-ray and biventricular hypertrophy on ECG were observed. Echocardiography revealed poor contractility and severe left ventricle hypertrophy. Muscle biopsy showed vacuolated lymphocytes containing glycogen and enzyme analysis confirmed Pompe disease. ERT with recombinant human acid α-glucosidase had already been given (20 mg/kg IV every second week) (Genzyme Therapeutics, UK) from 6 weeks of age and treatment for cardiac failure was commenced. Respiratory failure worsened and noninvasive ventilation was offered on the pediatric intensive care unit (PICU). He became fully dependent on continuous positive airway pressure (CPAP) despite optimization of fluid status. Rapid deterioration occurred on day 5 with a brief cardiac arrest and thereafter, invasive ventilation for 5 days. Subsequent improvement allowed extubation to CPAP. Examination revealed axial and peripheral hypotonia with only minimal antigravity movement. The child was fully conscious with a normal EEG but was only able to interact with his parents to a limited degree. This led to concerns about the psychological well-being of the infant with frequent episodes of what appeared to be distress resistant to standard analgesics. No improvement in motor function was demonstrated despite regular physiotherapy and neurologic assessment, ERT continued throughout.

Concerns over the continued treatment of this child were frequently raised but were met by the opinion that he must be allowed to benefit from ERT and that an indeterminate amount of time should be offered for the therapy to work. In the meantime full ventilator support should be offered. On day 103 of PICU admission he became pyrexial and within 24 hours he developed severe sepsis, had a cardiac arrest, and died. This was not considered an adverse drug reaction, as ERT had not been given for 4 days.

Case 2. A premature infant with Down syndrome was slow to wean from her ventilator after duodenal atresia repair. Infantile Pompe disease was diagnosed following echocardiography, and confirmed by enzyme analysis. ERT was commenced despite congenital abnormalities being specifically excluded in the reported study.[3] A discussion was held among the metabolic medicine service, PICU, and her parents. It was suggested that PICU in the setting of cardiorespiratory deterioration was not in her best interests. While the Down syndrome would undoubtedly contribute to muscular weakness, it did not form the basis for the decision-making process, rather it was suggested the fact that no data existed regarding any contribution of ERT to the prognosis of ventilated infants with Pompe was key. It was decided that admissions for specific indications such as central line insertion might be appropriate, but that any admission in the context of generalized Pompe cardiorespiratory deterioration was wrong. Despite the above discussion the child was ventilated at her local neonatal unit and died at 6 weeks of age.

Discussion. Our cases represent the most severe form of infantile Pompe disease presenting with re-

spiratory failure soon after birth and requiring mechanical ventilation. While the efficacy of ERT in preventing early death in infantile Pompe has been reported in a nonventilated group of infants,[3] there are no reports of the successful use of ERT in ventilated neonates or infants. In both our cases there was pressure to offer indefinite mechanical ventilation in the hope that ERT would eventually work.

ERT has improved survival in Pompe disease. However, it has not been shown to affect outcomes in the most severe cases presenting in the first few months of life with associated congenital anomalies or ventilator dependence. This raises the question whether neonates receiving ERT should be offered mechanical ventilation. We suggest that serious consideration be given before offering ERT to neonates and infants who are already on mechanical ventilation, or on the verge of requiring ventilation.

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