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NEURO CUTANEOUS MELANOSIS ASSOCIATED WITH AUTOIMMUNE DIABETES MELLITUS

Case report. A 12-year-old boy with multiple nevi presented with 6 months of polydipsia (>4 L/day), polyuria, and a 40-pound weight loss that progressed over weeks to intractable headache and vomiting. The patient subsequently developed ataxia, complex partial seizures, and encephalopathy. Medical history was significant for numerous (40 to 50) benign congenital nevi ranging in diameter from 1 to 10 cm. He did not have a previous diagnosis of neurocutaneous melanosis (NCM) or a history of CNS disease. The initial workup revealed hyperglycemia (random blood glucose of 400) and hemoglobin (Hgb) A1c 11.9%. Anti-glutamic acid decarboxylase (GAD) antibody was 2.1 U/mL (normal <0.1). There was diffuse leptomeningeal enhancement on MRI. Initial lumbar puncture revealed an opening pressure of 40 cm H₂O, white blood cell count of 23, glucose 40, and protein 193. Cytology from the CSF demonstrated atypical melanocytes consistent with malignant melanoma (figure). EEG showed epileptiform activity in the right mid-temporal cortex. Dermatologic evaluation of the congenital nevi revealed stable lesions without evidence of malignant transformation.

The presence of CNS melanoma and numerous congenital melanocytic nevi confirmed the diagnosis of NCM. The patient was treated with whole-brain radiation, interferon, temozolamide, diamox, and phenytoin. He had a peak insulin requirement of insulin glargine 15 units qhs and insulin aspart ac. Repeat serum evaluation revealed blood glucose of 90, HgbA1C 5.3%, and undetectable anti-GAD antibody (<0.1). His headache and tremor resolved without recurrence. He had a breakthrough seizure that prompted the addition of levetiracetam. After 6 months of diabetes mellitus (DM) management, our patient no longer required insulin to maintain normoglycemia. The skin lesions remained stable throughout the course of his disease without evidence of malignant transformation. Our patient never demonstrated evidence of spread of his melanoma beyond the CNS. The patient subsequently developed progressive cachexia, a large midline ce-

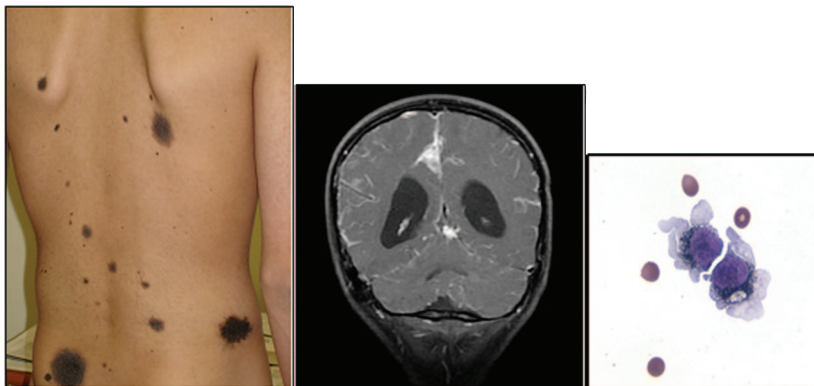
rebral mass, and left-sided hemiparesis with increased seizure activity. He died 14 months after the start of therapy.

Discussion. NCM is a rare congenital dysplasia of neural crest cells characterized by midline nevi and melanocytic infiltration of the CNS.^{1,2} Patients typically present in early childhood with rapidly progressive symptoms from increased intracranial pressure secondary to leptomeningeal melanosis or melanoma. Prognosis for patients with symptomatic NCM is uniformly poor, with approximately 6.5 months median survival time after onset of symptoms.³ Patients with symptomatic NCM and leptomeningeal spread of melanoma are thought to have a significantly worse prognosis.

GAD is expressed in neurons and islet cells of the pancreas. Anti-GAD antibodies have been described in type 1 and 2 DM,⁴ stiff person syndrome, cerebellar ataxia, and paraneoplastic syndromes.⁵ Anti-GAD antibodies have also been described as a paraneoplastic phenomenon in renal cell carcinoma,⁶ pancreatic tumor, and thymoma. Although the overall incidence of anti-GAD antibodies in autoimmune DM is not known, these antibodies are present in 80% of patients with type 1 DM and less than 2% of normal subjects. The association of NCM with insulin-dependent diabetes and anti-GAD antibodies has not been previously observed.

We report a case of NCM presenting in a 12-year-old boy with symptoms of new-onset insulin-dependent diabetes. The resolution of his insulin requirement and loss of anti-GAD antibodies coincided with treatment of his CNS malignant melanoma, suggesting a paraneoplastic autoimmune phenomenon. The association between autoimmune paraneoplastic processes and prolonged survival has been described in non-NCM patients with melanoma.⁷ For nearly 18 months since the onset of polydipsia and 14 months from the start of chemoradiation therapy, the patient remained alive and remarkably functional. We therefore suspect that despite the major CNS involvement and condition on presentation, the patient's prolonged clinical course may be due in part to autoimmunity.

Figure MRI and cytology findings



(A) Multiple large congenital melanocytic nevi. (B) Coronal T1 post-gadolinium MRI of the brain demonstrating diffuse leptomeningeal enhancement and right parasagittal cortical enhancement. (C) Atypical pleomorphic cells with melanin pigment in CSF, consistent with malignant melanoma.

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LAMBERT-EATON MYASTHENIC SYNDROME WITH PURE OCULAR WEAKNESS

Complaints of double vision or droopy eyelids have been reported in 0 to 65% of patients with Lambert–Eaton myasthenic syndrome (LEMS), although in none of these series was it the only complaint.^{1–3} Two cases of patients with solely ocular complaints initially but an overlap of LEMS and myasthenia gravis (MG) have been previously reported.^{4,5} This is a report of an LEMS patient with weakness limited to ocular muscles.

Case report. A 52-year-old woman presented with an 8-month history of diplopia starting abruptly and initially constant. Subsequently, it became intermittent and evoked by lateral gaze. She noticed occasional droopiness of her eyelids. Her only other recent complaints were fatigue and a 19-pound weight gain over 1 year, which she attributed to lacking the energy to exercise. Dry mouth had been present for several years. She was disabled by rheumatoid arthritis, which had affected multiple other family members. She smoked one and a half packs of cigarettes per day for the past 32 years. She had been seen previously by a neurologist and had a number of studies already performed. Binding, blocking, and modulating acetylcholine receptor antibodies were negative; thyroid function and creatine kinase level were normal. Brain MRI was nor-

mal. Deltoid muscle biopsy sample showed a few ragged red fibers appropriate for age.

On cranial nerve examination, with lateral gaze, she reported fuzzy, but not double images after 20 seconds. With right gaze, she immediately developed right ptosis, and with left gaze, her left lid started to droop after several seconds. Motor strength examination in both upper and lower extremities was normal. She could rise from a chair with ease and squat down and up without using her hands. Heel and toe walking was done without difficulty. Reflexes were two and symmetric throughout. Toes were downgoing. Sensory examination was normal to vibration, joint position sense, and pinprick. Forced vital capacity was 65% of predicted.

Electrophysiologic testing was performed. Her right median compound muscle action potential (CMAP) amplitude (measured baseline to peak) was 2.3 mV (normal ≥ 5 mV) and right ulnar was 3.4 mV (normal ≥ 5 mV). Conduction velocities and F-wave latencies were normal. The right median motor and sensory distal latencies were mildly prolonged, consistent with right carpal tunnel syndrome. The remaining sensory studies including amplitudes were normal, and ulnar motor distal latency was normal. Following 10 seconds of exercise, her right ulnar CMAP increased to 6.8 mV or by 100%. Repetitive nerve stimulation of the right ulnar nerve at 3 Hz

resulted in a 17% decrement in the CMAP amplitude, which did not change significantly following 1 minute of exercise. A train of 20 stimuli delivered at 50 Hz resulted in a 164% amplitude increment. The diagnosis of LEMS was made. P-type voltage-gated calcium channel antibodies were positive (performed by Quest Diagnostics, San Juan Capistrano, CA); Q type was not tested. A CT scan of the chest revealed several enlarged lymph nodes in the mediastinum. A biopsy specimen revealed small cell lung cancer. She was treated with chemotherapy with resolution of her ocular complaints. It is now 14 months since the discovery of her cancer, which is now in remission, and the patient has had no recurrence of neurologic symptoms.

Discussion. Reports of patients with LEMS and symptoms initially limited to ocular complaints are rare. The earliest case predated antibody testing, and the combined diagnoses of LEMS and MG were based on electrophysiology and response to medications.⁵ The patient in that case had ophthalmoplegia and normal extremity strength. Although hyporeflexic, he also had an underlying sensory neuropathy. No underlying malignancy was identified. The other reported patient⁴ presented with ocular symptoms and had mild elevation of acetylcholine receptor antibodies and was diagnosed with MG. He was diagnosed 6 months later with LEMS when he developed lower extremity proximal weakness and dry mouth. Voltage-gated calcium channel antibodies were positive, and the acetylcholine receptor antibodies had disappeared. An early clue may have been his areflexia at initial presentation, not uncommon with LEMS.¹⁻³

This patient described here was referred for the question of antibody negative ocular MG. She had

neither proximal weakness nor hypo- or areflexia typical of LEMS¹⁻³ and had paradoxically gained weight. Her sole autonomic symptom, dry mouth, was not new. Small CMAP amplitudes on nerve conduction studies with an increment following exercise and with 50-Hz stimulation demonstrated the presynaptic nature of the disorder. The possibility remains that if her cancer recurs, more typical LEMS symptoms and signs may develop. This case demonstrates that, albeit rare, patients suspected of having antibody-negative ocular MG need to have LEMS also included in the differential diagnosis.

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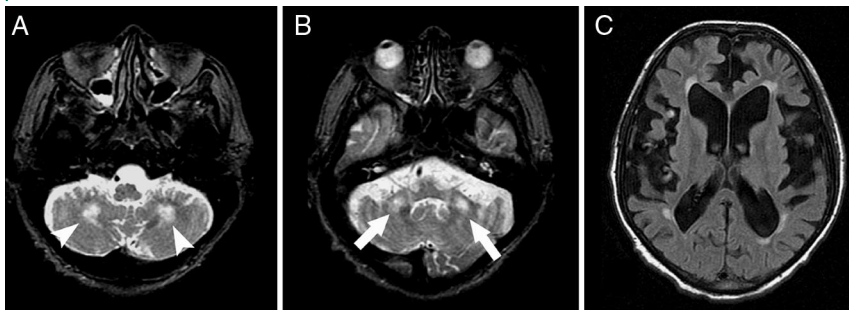
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ATYPICAL CLINICAL COURSE OF FXTAS: RAPIDLY PROGRESSIVE DEMENTIA AS THE MAJOR SYMPTOM

The fragile X–associated tremor/ataxia syndrome (FXTAS) is a progressive neurologic disorder that may affect carriers of premutations of the *FMR1* gene (55 to 200 CGG repeats), mainly men older than 50 years of age. These individuals do not have the mental retardation syndrome, which is caused by the *FMR1* gene full mutation (>200 CGG repeats). The major FXTAS features include progressive intention tremor and cerebellar ataxia, often accompanied by progressive cognitive and behavioral disturbances, such as memory loss, anxiety, deficits of executive functions, and reclusive or irritable behavior, with a gradual appearance of

dementia in some individuals; parkinsonism, peripheral neuropathy, lower-limb proximal muscle weakness, and autonomic dysfunction may be present.¹ Severe dementia has been seen in a limited number of patients.² Neuropsychological assessments in 29 FXTAS patients revealed that 21% had Full Scale IQs <85, reflecting severe cognitive impairment or dementia.³ Neuropsychiatric manifestations (agitation/aggression, depression, apathy, disinhibition, and irritability) compatible with frontal-subcortical dementia were documented as significantly greater in patients with FXTAS vs normal age-matched controls.⁴ The major neuroimaging criterion for FXTAS diagnosis is hyperintensity of the middle cerebellar peduncle (MCP sign) on T2-weighted MRI.¹ Analyses of brains from

Figure MRI findings



Axial T2-weighted images demonstrate bilateral hyperintense lesions in cerebellar white matter (arrowheads in A) and middle cerebellar peduncles (arrows in B). Note also, in an axial fluid-attenuated inversion recovery image, moderate prominence of the lateral ventricles and enlarged sylvian fissures associated with scarce hyperintense foci in cerebral white matter (C).

patients who died with this disorder revealed eosinophilic intranuclear inclusions in neurons and astrocytes, which predominated in the hippocampus and frontal cortical regions.²

The severity and progression of FXTAS are variable, and, although the clinical symptoms in many individuals remain relatively stable for decades, in others, the course of the disease is rapid, with death occurring 5 to 6 years after the onset of symptoms, a probable reflection of the genetic or environmental background of the carriers.³ Herein we describe a 70-year-old man carrying a premutation and showing severe progressive dementia and mild gait ataxia without intention tremor. The neuroimaging signs in association with the premutation made FXTAS diagnosis the most likely, despite the unusual clinical presentation of the disease.

Case report. The patient was ascertained in a fragile X family; he was the maternal grandfather of a mentally retarded boy, the proband, who carried a full mutation of the *FMR1* gene. PCR analysis of the CGG repeat⁵ revealed a (CGG)₈₅ allele, a premutation of the *FMR1* gene, whereas the proband's grandmother carried (CGG)₂₀ and (CGG)₂₉ alleles, in the normal range of variability. The proband's mother was a premutation carrier and suffered premature ovarian failure at 31 years of age. Premature ovarian failure is recognized as a manifestation of the premutation.⁶

The patient had no schooling in the poor region where he lived and worked as a mason. The reason for his retirement 8 years before the onset of the symptoms was not related to cognitive problems. At age 69 years, apparently simultaneously, he experienced the onset of reclusive, apathetic behavior and gait difficulties characterized by imbalance. Neurologic examination 1 year later revealed severe cognitive impairment; he scored 11/30 on the Mini-Mental State Examination. On the Dementia Rating Scale, he scored 70/144, with severe deficits of attention and initiation/perseveration, suggestive of

frontal-subcortical network involvement. He also showed mild gait ataxia, Babinski sign, increased facial jerks, and bilateral palmomental reflex. Urinary incontinence was reported. MRI (figure) disclosed symmetric T2-hyperintense white matter lesions involving the middle cerebellar peduncle (MCP sign) and the cerebellar hemispheres associated with diffuse brain atrophy.

Discussion. This patient had no tremor or limb ataxia and only mild gait ataxia, but presenting with major (MCP sign) and minor (generalized brain atrophy) FXTAS neuroimaging signs¹ associated with executive dysfunction and very severe cognitive impairment. Although the clinical course may vary, the prominent FXTAS symptom in the early stages is intention tremor followed by gait ataxia, parkinsonism, peripheral neuropathy, and cognitive decline particularly affecting executive functioning and later severe motor deficits.³ However, in the patient described here, cognitive impairment was the major clinical sign in contrast with mild motor symptoms, and although cognitive deficits progressed rapidly in 1 year, the motor symptoms remained unchanged.

An atypical rapid course of progressive dementia was described in a male carrier of a (CGG)₉₃ premutation allele, whose clinical features also included tremor, ataxia, parkinsonism, and brain white matter changes.⁷ Postmortem pathologic findings were compatible with the diagnosis of FXTAS as well as of Alzheimer disease (AD). A pathologic condition other than FXTAS might also explain the rapidly progressive cognitive deficit in our patient, but the absence of hippocampus atrophy, as documented by MRI, and the very rapid progression of the cognitive decline make AD improbable.

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