Fragile X-associated tremor/ataxia syndrome presenting in a woman after chemotherapy

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Fragile X–associated tremor/ataxia syndrome presenting in a woman after chemotherapy

J.P. O'Dwyer, MRCPI; C. Clabby, PhD; J. Crown, MD; D.E. Barton, PhD; and M. Hutchinson, FRCP

Fragile X, the most common inherited cause of mental retardation, is an X-linked disease with expansion of triplet repeats (>200 CGG repeats) of the fragile X mental retardation-1 gene (FMR1). This encodes for a protein (FMRP) highly expressed in neurons, whose normal role has been linked to G-quartets and regulation of microtubule associated protein 1B mRNA translation.[1] Alleles exist in an unmethylated active state, including those in the premutation range (55 to 200 CGG repeats).

A new syndrome, the fragile X–associated tremor/ataxia syndrome[2] (FXTAS), seen in male carriers of the premutation, is characterized by tremor, gait ataxia, cognitive deficits, and in some patients, by parkinsonian signs. The onset of FXTAS is from the fifth decade and half of those affected have high signal intensity abnormalities on T2W MRI in the middle cerebellar peduncles. Few women have been described with this disorder.

We report a woman carrier of the FMR1 gene in the premutation range, who presented with tremor and severe gait ataxia following treatment with carboplatin-containing chemotherapy.

Case report. A 70-year-old right-handed woman with history of HER-2 over-expressing breast carcinoma was diagnosed with hepatic metastases. She had not previously seen a neurologist, but her husband had noticed a clumsy gait and head tremor in the last few years. She had two sons with fragile X mental retardation syndrome. Eight days after the first cycle of 3-weekly docetaxel (75 mg/m^2) and carboplatin (4 mg/mL.min), with weekly trastuzumab (2 mg/kg), she developed nausea and weakness. On day 11, she had sudden onset of profound ataxia, with upper limb and head tremor.

On examination there was mild titubation, with a postural tremor of the upper limbs, and mild finger/nose ataxia. There was moderate heel/toe and severe gait ataxia. She could not stand unaided, and could not walk. There was no nystagmus, dysarthria, or rigidity. Investigations included a brain MRI, which showed mild cerebellar atrophy (figure). There was no evidence on T2 or FLAIR of high signal in the middle cerebellar peduncle, the white matter abnormality seen in almost half of FXTAS cases. Cytotoxic chemotherapy was withheld.

On examination at day 67, she had mild titubation, tremor of the extended arm, finger/nose ataxia, and hypomimia. There was moderate heel/shin ataxia bilaterally. She was walking independently with a broad-based gait but was unable to tandem walk. She and her husband felt she had returned to her baseline state. The CAMCOG score was 70 indicating mild global cognitive impairment; there were marked dysexecutive features (executive subscore 5/28). CAMCOG is the cognitive portion of the Cambridge mental disorders of the elderly examination.[3] The maximum CAMCOG score is 105; 60 to 80 indicates mild cognitive impairment. Docetaxel alone was reinstituted on day 42, without exacerbation of signs.

DNA from a peripheral blood sample was tested for the fragile X premutation by PCR and southern blotting. Southern blotting identified one allele in the normal range and a second allele of approximately 95 CGG repeats.

Discussion. This woman presented with a severe cerebellar ataxia and tremor following chemotherapy. This improved, returning to her pre-chemotherapy state of mild ataxia and intention tremor. We postulate that the FMR1 premutation state made this woman vulnerable to the toxic effects of carboplatin-containing chemotherapy, resulting in an acute cerebellar syndrome.

Pure cerebellar semiology is rarely reported with platinum compounds, being generally restricted to patients who receive high doses. Carboplatin crosses the blood–brain barrier and is transported intracellularly. In vitro, carboplatin slows microtubule disassembly. In this case, the toxic effect could be related to background microtubule dysfunction from lower levels of FMRP.

Transient post-administration encephalopathy rarely occurs following taxane therapy. In our patient, docetaxel was well tolerated. Breast cancer itself may rarely be associated with paraneoplastic cerebellar degeneration in which antibodies are produced against cytoplasmic Yo or Ri proteins in cerebellar Purkinje cells, either directly or via a cytotoxic T-cell response. It is generally resistant to treatment, progressively deteriorating.[4]

The association of neurologic signs in female premutation carriers is less marked than that found in men.[5] However, clearly FXTAS does occur in women.[6]

The premutation prevalence in women is estimated to be 1 in 259. Abnormal eosinophilic polyglutamine-negative intraneuronal inclusions have been identified at autopsy in four men with the premutation, and more recently in one woman.[6] A murine model has shown identical lesions, particularly affecting the granular layer of the tenth cerebellar lobule.[7]

This case suggests the possibility that patients with subclinical carriage of the fragile X premutation gene might develop FXTAS following exposure to carboplatin chemotherapy.

From the Departments of Neurology (Drs. J.P. O'Dwyer and Hutchinson) and Medical Oncology (Dr. Crown), St. Vincent's University Hospital; and National Centre for Medical Genetics (Drs. Clabby and Barton), Our Lady's Hospital for Sick Children, Dublin, Ireland.

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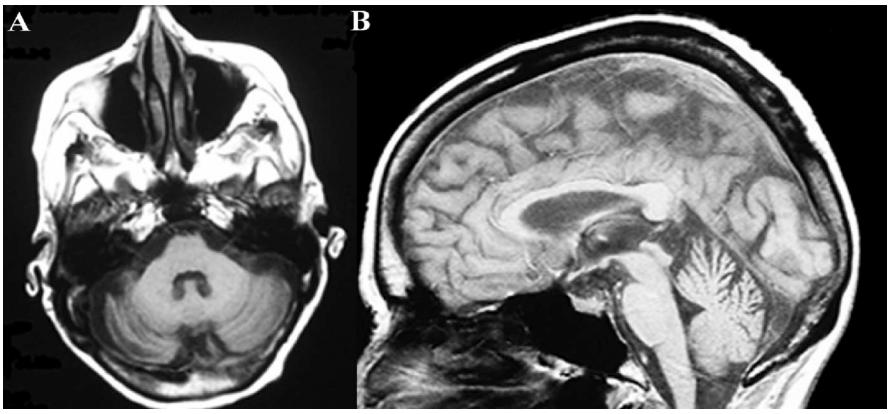

Figure. T1-weighted axial (A) and sagittal (B) MRI showing mild atrophy of the cerebellar vermis and cortex.

Editorial, see page 190
See also page 299

Address correspondence and reprint requests to Dr. J.P. O'Dwyer, Department of Neurology, St. Vincent's University Hospital, Dublin 4, Ireland; e-mail: drjpodwyer@eircom.net

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Systemic mastocytosis: A potential neurologic emergency

G.B. Boncoraglio, MD; A. Brucato, MD; M.R. Carriero, MD; E. Maccagnano, MD; L. Robbiolo, MD; L.O. Scappatura, MD; D. Soligo, MD; and E.A. Parati, MD

Mastocytosis refers to an uncommon and heterogeneous group of clonal hematologic disorders characterized by pathologic accumulation of mast cells (MCs) in various tissues. In 80 to 90% of cases, abnormal MC infiltration is restricted to the skin (cutaneous mastocytosis) and appears as small discrete red–brown maculae (urticaria pigmentosa); prognosis is favorable. By contrast, multifocal MC accumulation in extracutaneous organs (systemic mastocytosis [SM]) is potentially life threatening; the skin may or not be involved.[1] The presenting signs and symptoms of SM are due to pathologic infiltration of MCs and release of their chemical mediators, primarily histamine. Typical clinical features include urticaria pigmentosa, hepatosplenomegaly, bone pain, headache, flushing, pruritus, nausea, diarrhea, abdominal pain, and peptic ulcer. Sudden transient loss of consciousness and hypotensive or anaphylactic shock may also occur.[2] Patients with undiagnosed SM can also present with neurologic symptoms.[3] We describe a 64-year-old woman with unexplained recurrent episodes of loss of consciousness and neuroradiologic signs of chronic brain ischemia, who developed severe anoxic encephalopathy after hypotensive shock due to SM.

Case report. The patient was admitted to our institute in September 2003. She reported a regular lifestyle, duodenal ulcer diagnosed at age 25, and allergy to acetylsalicylic acid. She had had a nonpruritic maculopapular rash on both legs and trunk since age 56 and recurrent episodes (about every 2 months) of flushing, palpitations, epigastric discomfort, and vomiting, sometimes followed by loss of consciousness for a few minutes with spontaneous recovery. For 2 to 3 days after these episodes, she experienced diffuse musculoskeletal pain and fatigue. In one episode, teeth grinding and incontinence occurred. In January 2003, she had had a sudden collapse followed by transient comatose state: hypotension and ST elevation were present on EKG, while echocardiography, coronarography, blood markers of cardiac ischemia, Holter EKG, and pulmonary scintigraphy were normal. Brain MRI revealed signs of chronic ischemic encephalopathy. In June 2003, she experienced acute transient loss of consciousness followed by confusion, loss of coordination, alexia, and agraphia.

She was admitted to our institute for differential diagnosis between epilepsy and cerebrovascular disease due to heart condition or vasculitis. Physical and neurologic examinations were unremarkable except for multiple macular hyperpigmented lesions on the trunk and legs (figure). Blood tests were normal. On the second day, the patient developed sudden severe hypotensive shock followed by comatose state. Initially there was no palpable carotid pulse. A few days later, she recovered alertness but had global aphasia and spastic tetraparesis. Brain MRI showed acute anoxic encephalopathy (see figure). The skin biopsy finding (focal infiltrates of MCs) and the high serum tryptase level (156 ng/mL) were consistent with mastocytosis. After bone marrow biopsy and aspiration, SM with associated monolinear myelodysplasia was diagnosed. H1- and H2-Histamine receptor antagonists, sodium cromoglycate, baclofen, and risperidone were started. However, 5 months later, the patient had totally lost her independence, had fecal and urinary incontinence, and had received percutaneous endoscopic gastrostomy; brain MRI showed remnants of the acute anoxic encephalopathy (see figure).

Discussion. The clinical presentation of SM is extremely heterogeneous and may include loss of consciousness, seizures, cerebrovascular accident, headache, dizziness, or even transient chorea.[3-5] Thus, undiagnosed SM may come to the attention of neurologists. The neurologic signs and symptoms seem more likely due to a direct effect of MC mediators or to hypotension than to MC infiltration of the CNS.[4,5] However, death after rapid neurologic deterioration with postmortem demonstration of multiple cerebral infarcts with intravascular microthrombi and cerebral invasion by eosinophils (suggesting vasculitis) has been described.[6] Recurrent syncope with fatal hypotensive shock has also been reported.[7]

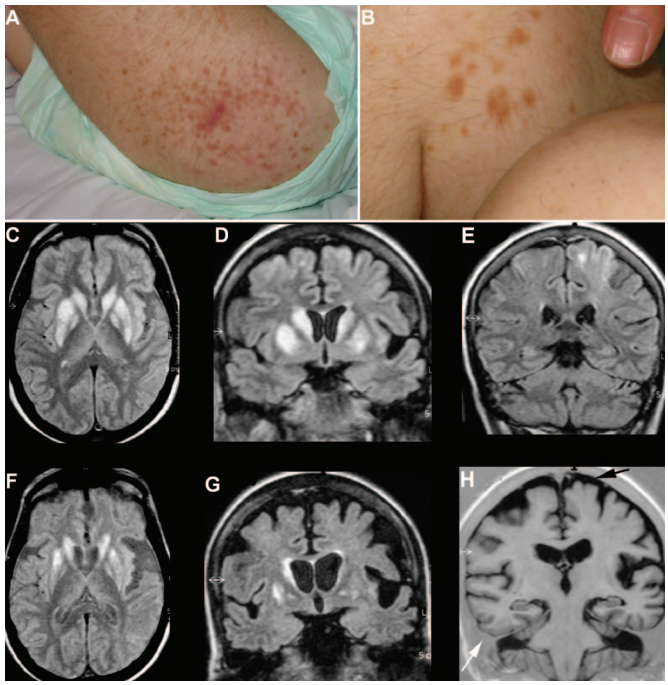

Figure. (A and B) Urticaria pigmentosa appears as multiple macular hyperpigmented lesions, here on the left leg and right knee. (C through E) MRI in acute phase of anoxic encephalopathy: Axial proton density (PD) (C) and coronal fluid-attenuated inversion recovery (FLAIR) (D, E) images show high-intensity lesions involving basal ganglia (in particular putamen, globus pallidus, and caudate bilaterally) and frontoparietal cortex. (F through H) Five months later, axial PD (F), coronal FLAIR (G), and inversion recovery (H) images show that the hyperintense lesions of the basal ganglia are reduced, the frontal horns of the lateral ventricles are enlarged, and the frontoparietal cortex has atrophied (black arrow) with loss of normal signal intensity and enlargement of cerebral sulci (white arrow).

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