Hepatitis B reactivation during glioblastoma treatment with temozolomide: A cautionary note

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We diagnosed a 50-year-old right-handed Chinese man with a right temporal glioblastoma in October 2005, after he presented with headaches and progressive left hemiparesis. He had no significant past medical illnesses and no known history of hepatitis, blood transfusion, or IV drug use. He had immigrated to the United States 5 years previously from Shanxi Province, China. He had a craniotomy with gross total tumor resection. He was discharged on rapid dexamethasone taper beginning at 24 mg total a day; 2.5 weeks later, he was on dexamethasone 4 mg total a day.

Three weeks postresection, he began radiotherapy (60 Gy in 30 fractions over 6 weeks) together with 6 weeks of daily temozolomide (75 mg/m²/day). Liver function tests (LFTs) were normal just prior to chemotherapy and radiation, except an SGPT 68 U/L (normal 7 to 56 U/L) (figure). During chemo-radiation therapy, the nadir of white blood cell count was 5.3 K/µL, absolute neutrophil count 3.89 K/µL, and absolute lymphocyte count 0.58 K/µL. Throughout chemo-radiation, his dexamethasone continued at 4 mg total a day; thereafter he tapered down to 0.5 mg total a day.

One week post-radiation, he developed worsening left hemiparesis as a result of a subdural collection. His dexamethasone dose was briefly increased from 0.5 mg daily to 2 mg daily. We noticed elevated LFTs (figure).

We report the case of a Chinese man with a right temporal glioblastoma who received radiotherapy with concomitant temozolomide, together with lamivudine, erlotinib.

Discussion. Worldwide, an estimated 350 million people are chronic hepatitis B carriers, with approximately 170 million carriers in China and 1.25 million in the United States, most of whom are asymptomatic. Immunosuppressive cytotoxic chemotherapy increases the risk for hepatitis B reactivation, especially in patients with lymphoma or breast cancer, those with detectable prechemotherapy HBV DNA load, or whose treatment includes corticosteroids or antithrombinase.

Prophylactic lamivudine during and for 6 months after treatment has been safely administered in hepatitis B carriers with predominantly hematologic malignancies and should be considered in cancer patients who are carriers. We describe a case of hepatitis B reactivation in a man with glioblastoma who received radiotherapy with concomitant temozolomide and low-dose corticosteroids. The relatively unremarkable liver tests on October 28, 2005, and subsequent positive tests for HBsAg, HbcAb IgG, and HBeAb indicated the patient was an inactive hepatitis B carrier. Chemotherapy is known to activate hepatitis B in cancer patients. Since his steroid dose was low, it is likely the immunosuppression from temozolomide played the predominant role in viral reactivation; however, we cannot be completely certain that steroids had no role in our particular case. There are two putative mechanisms of hepatitis B virus reactivation during chemotherapy: immunosuppression from chemother-

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**Table: Liver function test trend with respect to temozolomide chemotherapy and lamivudine treatment.**

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<tr>
<th>Date</th>
<th>SGOT (IU/L)</th>
<th>SGPT (IU/L)</th>
<th>ALK phosphatase (IU/L)</th>
<th>Hepatitis B surface antigen (HBsAg)</th>
<th>Hepatitis B core antibody (HBCa IgG)</th>
<th>Hepatitis B core antibody (HBCa IgG)</th>
<th>Hepatitis B e antibody (HBeAb)</th>
<th>Hepatitis C antibody (HCVAb)</th>
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**Figure.** Liver function test trend with respect to temozolomide chemotherapy and lamivudine treatment. a Normal ranges for the Dana-Farber Cancer Institute laboratory are as follows: serum bilirubin 0.2 to 1.3 mg/dL, SGOT 14 to 46 U/L, SGPT 7 to 56 U/L, alkaline phosphatase 38 to 126 U/L. b Normal ranges for the Brigham and Women’s Hospital laboratory are as follows: serum bilirubin 0.2 to 1.2 mg/dL, SGOT 9 to 30 U/L, SGPT 7 to 52 U/L, alkaline phosphatase 36 to 118 U/L. When dexamethasone dates have a ~ symbol, it indicates that steroids were changed over several days to the noted dose.
apy enhances virus replication leading to hepatic toxicity; or chemotherapy-induced T-cell depletion dampens host response to viral antigens and allows broader hepatocyte infection. When the chemotherapy is withdrawn (in our case, at the end of the 6 weeks of temozolomide), the rebound immune response causes hepatocyte destruction. Since 2005, the standard treatment for glioblastoma has been radiotherapy with 6 weeks of daily low-dose concomitant temozolomide, followed by 6 months of adjuvant temozolomide. Protracted daily temozolomide dosing is associated with lymphopenia and an increased risk of opportunistic infections such as *Pneumocystis pneumonia*. Although reactivation of hepatitis B infection has not been reported previously in patients with brain tumor undergoing chemotherapy, the widespread use of prolonged daily dosing of temozolomide is likely to increase the incidence of this complication. To avoid this, patients at risk of hepatitis B—either those who come from endemic areas or those who have high-risk behaviors—should be considered for hepatitis B screening prior to initiating temozolomide chemotherapy. If the test for hepatitis B DNA reveals elevated levels, patients should receive prophylactic therapy with agents such as lamivudine, adefovir, or entecavir—all active against hepatitis B—for at least 2 months after chemotherapy. Finally, in chemotherapy patients with elevated LFTs, physicians should include viral hepatitis in the differential diagnosis, along with medication-induced hepatotoxicity.

**References**


**Case report.** A 69-year-old man with a history of hypertension developed acute vertigo with nausea/vomiting and postural imbalance. On examination, we observed spontaneous horizontal nystagmus in the primary position which reversed its direction with a cycle of approximately 2 minutes and a transition period of several seconds by using video Frenzel goggles (SLMED, Seoul, Korea) (see the video on the Neurology Web site at www.neurology.org). The horizontal nystagmus remained in up- and down-gazes with decreased amplitude. Periodic head turn was not observed. With fixation, the nystagmus disappeared. Downbeat nystagmus was induced for about 10 seconds by horizontal head-shaking for 20 seconds (video). Gaze-evoked nystagmus or saccadic dysmetria was not observed. Horizontal and vertical smooth pursuit appeared to be normal for his age. Horizontal head thrust tests were normal. His gait was ataxic, but no limb dysmetria was present on finger-to-nose and heel-to-shin test.

Somatosensory and brainstem auditory evoked potentials and audiogram were normal. Bithermal caloric tests showed symmetric responses. Sinusoidal harmonic accelerations (peak velocity: 50 °/second, frequency range: 0.02 to 0.32 Hz) showed normal gains and phases of the vestibulo-ocular reflex (VOR). Time constants (TCs) of the per- and postrotatory nystagmus during step velocity rotations (peak velocity: 100 °/second, acceleration and deceleration: 100 °/second2, duration: 60 seconds) were mildly increased at 19.3 seconds (normal: 14.7 seconds) and TCs of the postrotatory nystagmus were not suppressed by forward head tilt (mean: 18.0 seconds). Diffusion-

**VIDEO** Periodic alternating nystagmus in isolated nodular infarction

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Periodic alternating nystagmus (PAN) is characterized by periodic reversal of horizontal jerk nystagmus with a null period of several seconds. Damage to the uvulonodulus or to their connections with the brainstem vestibular nuclei has been suggested as a mechanism of PAN. However, PAN has rarely been reported in circumscribed cerebellar lesion.

We report a patient with isolated nodular infarction who developed PAN without fixation in association with perversed head-shaking nystagmus (HSN) and loss of tilt suppression of the postrotatory nystagmus. This is the first report of PAN in circumscribed cerebellar infarction, and provides further evidence that PAN occurs due to dysfunction of cerebellar nodulus.

Additional material related to this article can be found on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the March 20 issue to find the title link for this article.

Figure. Diffusion-weighted (A) and T2-weighted imaging (B) of MR shows an acute infarction restricted to the cerebellar nodulus.
weighted MRI disclosed a circumscribed acute infarction in the cerebellar nodulus (figure). Other parts of the cerebellum and the brainstem were intact. Over the following several days, vertigo, PAND, and postural imbalance resolved.

Discussion. We observed PAND, perverted HSN, and impaired tilt suppression of the postrotatory nystagmus in a patient with isolated nodulus infarction. In monkeys, ablation of the cerebellar nodulus gave rise to PAND in darkness. Since the nodulus normally inhibits the time course of rotationally induced nystagmus, i.e., the velocity storage mechanism, PAND has been ascribed to prolonged vestibular response after uvulonodular damage, and reversal of the nystagmus by normal vestibular repair mechanism, which would result in periodic oscillation of PAND.\(^4\)\(^5\)

The postrotatory nystagmus is normally suppressed by head tilting, after cessation of step-velocity rotation (tilt suppression). This suppressive effect is lost after ablation of the uvulanodulus.\(^6\)\(^7\) Indeed, in our patient, TCs of the per- and postrotatory nystagmus were mildly increased to an average of 18.3 seconds. Furthermore, TCs of the postrotatory nystagmus were not diminished by head tilt after step velocity rotation.

In vestibulopathies, HSN can be induced by head oscillation at 2 Hz for approximately 20 seconds. In perverted HSN, HSN develops in another plane than that being stimulated by head oscillation. Perverted HSN is explained by abnormal cross-coupling of vestibular responses that have usually been attributed to lesions in the central vestibular pathways, including the vestibulocerebellum.\(^8\) The uvulanodulus are also known to control spatial orientation of the angular VOR and may participate in cross-coupling of the velocity storage during head tilt.\(^9\) Damage to these areas may induce abnormal activation of the cross-coupling during head oscillation and result in perverted HSN.\(^4\)

In our patient, PAND was present only without visual fixation. However, most of the previously reported cases of PAND showed little effect of visual fixation on the nystagmus. Cerebellar flocculus is important for suppression of vestibular nystagmus by visual fixation,\(^10\) and the disappearance of PAND with visual fixation in our patient suggests intact floccular function. The absence of saccadic dysmetria, gaze-evoked nystagmus, and spontaneous downbeat nystagmus in our patient is also consistent with the integrity of the oculomotor vermis and floccular region, and is suggestive of isolated nodular dysfunction.

Previously, multiple cerebellar and brainstem lesions or diffuse cerebellar atrophy have been reported with PAND.\(^1\)\(^2\) However, despite the numerous reports on nodular dysfunction as a mechanism of PAND, pathologic or radiologic confirmation of circumscribed nodular lesions has been unavailable in patients with PAND.\(^1\)\(^2\) PAND and associated findings in our patient with isolated nodular infarction provide further evidence that PAND develops due to nodular dysfunction.

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Disclosure: The authors report no conflicts of interest.

Received October 10, 2006. Accepted in final form November 27, 2006.

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References


Treatment-responsive pudendal dysfunction in chronic inflammatory demyelinating polyneuropathy

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A 48-year-old man presented with sensory disturbances in both hands and feet and difficulties when opening bottles or climbing the stairs. His symptoms had developed over 2 weeks and were preceded by fever of unknown origin. There was no history of toxin exposure. His past medical history was remarkable for Henoch-Schonlein purpura with nephritis and intestinal necrosis. Examination showed weakness of the neck, arm, and proximal leg muscles (Medical Research Council [MRC] grade 4). Vibration sense was diminished in both hands and feet, without a sensory level. Tendon reflexes were absent. There were no gastrointestinal symptoms, purpurae, or evidence of glomerulonephritis. Nerve conduction studies showed that the distal motor latency (DML) was increased in the median (5.6 milliseconds), ulnar (5.4 milliseconds), and peroneal nerves (19.2 milliseconds) and that the nerve conduction velocity (NCV) was decreased in the median (32 m/s) and peroneal (15.5 milliseconds) nerves, with conduction block and sural sparing.\(^1\) The CSF was normal. Screening about synphils was negative. The patient was diagnosed with Guillain–Barre syndrome (GBS) and was treated with IV gammaglobulin (IVIG; 0.4 g/kg daily for 5 days), which led to almost complete resolution of the muscle weakness within 3 weeks. Four weeks after discharge, the patient was readmitted with similar but more severe symptoms. In addition, he now reported fecal incontinence and a diminished anal reflex. The patient complained about new-onset erectile dysfunction, but urinary function was normal. There were no additional signs or symptoms of autonomic dysfunction. There was weakness of both arms and legs (MRC grade 3 to 4), absent distal vibration sense, and no tendon reflexes. Perianal sensation was normal, but voluntary sphincter contraction was nearly abolished. Nerve conduction studies showed an increased DML and a reduced NCV in the median, ulnar, and peroneal nerves on conduction block in the median nerve. There were no sural sensory nerve action potentials or ulnar F-responses. Concentric needle electromyography (EMG) of the external anal sphincter revealed a reduced recruitment pattern both at rest and during maximum contraction, without fibrillation potentials or positive sharp waves. Lumbar sacral magnetic stimulation showed an increased latency over the left pudendal nerve (20 milliseconds) and no response on the right. MRI of the lumbar spine was normal; nerve biopsy was not performed.

Anal manometry\(^2\) revealed a decreased resting pressure of the internal sphincter (32 mm Hg; normal = 2 SD 66 ± 46 mm Hg) and a decreased maximal squeeze pressure (a combination of internal and external sphincter function; 57 mm Hg vs normal 218 ± 140 mm Hg; figure). As a result, the maximal squeeze increment was nearly abolished (35 mm Hg; normal 90 ± 64 mm Hg), indicating impaired voluntary contraction of the external sphincter. Rectal sensitivity to balloon distension was not affected.

Under the revised diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP), the patient was again treated with IVIG. Three weeks later, muscle strength had increased, fecal incontinence had improved, and erectile function had returned to normal. Anal manometry showed a significant increase in resting pressure (to 51 mm Hg), maximal squeeze pressure (to 106 mm Hg), and maximal squeeze increment (to 80 mm Hg; figure). This was accompanied by an increase in NCV and a nearly normalized recruitment pattern on needle EMG. After 10 months, the patient had made a nearly full recovery and had no residual bowel or voiding symptoms. Treatment-responsive pudendal dysfunction in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). March 20, 2007 NEUROLOGY 68 957

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Multiple sclerosis: Relating MxA transcription to anti-interferon-β-neutralizing antibodies

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Interferon-β (IFNβ) treatment in multiple sclerosis (MS) induces neutralizing antibodies (NAB) in 10 to 30% of patients. NAB are associated with a reduction of bioactivity of IFNβ, and have a negative impact on therapeutic response. Analysis of IFNβ-inducible genes is a direct and practical approach to monitor therapy. The expression of three IFNβ-induced genes in antibody-positive patients with MS was recently analyzed. We performed a similar study to evaluate the relationship between the expression of myxovirus resistance protein A (MxA) and NAB activity. Our results confirm and extend previously reported results.

Methods. We collected serum and PAXgene (PreAnalytiX/Qiagen, Hilden, Germany) samples from 81 patients with relapsing-remitting MS (RR-MS) (54 women, 27 men, median age 38, Expanded Disability Status Scale [EDSS] median 2.0, range 0 to 6.5) before (n = 62) and 12 to 24 hours after (n = 71) injection of IFNβ (Avonex, n = 12; Rebif, 3 × 22 μg, n = 13; Rebif, 3 × 44 μg, n = 39; Betaferon, n = 17). Treatment duration was >6 months in all cases. We also collected blood samples from 25 untreated control patients with RR-MS (19 women, 6 men, median age 32 years, EDSS median 2.0, range 0 to 5.0). We analyzed transcription of MxA and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as suggested by ABI. NAB analysis was performed at Genter (Copenhagen, Denmark) using a previously described cytopathic effect assay (CPE), which measures the ability of NAB to counteract the protective effect of IFNβ when cultured human A549 cells (subclone MC-5) are exposed to a cytopathic IFNβ-sensitive virus (encephalomyocarditis virus). Results are reported as neutralizing capacity (NC), which represents the percentage of the added IFNβ (10 LU/mL) neutralized by the serum (5% v/v). All samples were tested for endogenous cytotoxicity and intrinsic antiviral activity. NC below 50% was regarded as negative, 20 to 70% as low positive, and 80% or above as high positive. The laboratory workers who performed the NAB assays were blinded with respect to the MxA transcription data, and vice versa.

Results. Within a time frame of 12 to 48 hours, pilot experiments (data not shown) showed maximum MxA transcription at 12 hours, with a moderate decrease at 24 hours postinjection (about 50 to 80% of the 12-hour values). At 24 to 48 hours MxA transcription further decreased, but was still above the basal levels observed in untreated MS and control subjects. Blood sampling before 12 hours postinjection is inconvenient for clinical routine purposes, as injections are usually given in the evening. Therefore...
we chose a time window of 12 to 24 hours for blood sampling after IFNβ injection.

We observed high positive NAB (>80% neutralizing capacity) in 9, low positive NAB (20 to 80%) in 5, and negative NAB activity (<20%) in 67 patients. Patients with high positive NAB (>80% neutralizing capacity) were divided as follows: Avonex 0/12, Betaferon 2/18, Rebif 7/52.

High levels of NAB (NAB<sup>high</sup>) were associated with very low MxA transcription, similar to untreated controls (figure, A; figure E-1 on the Neurology Web site at www.neurology.org). Patients with negative and low NAB activity (NAB<sup>neg/low</sup>) had 18-fold higher median MxA levels than untreated controls (figure, A).

We compared RNA extraction immediately after blood drawing and storage of full blood in PAXgene tubes for up to 5 days. The PAXgene system, which greatly simplifies the clinical application, proved to give similar MxA levels as the immediate RNA extraction (data not shown). Analysis of whole blood gave a similar sensitivity to detect IFNβ-mediated induction of MxA as analysis of separated immune cell subsets (monocytes, lymphocytes, neutrophils) (data not shown). Analyzing the after/before ratio of MxA values yielded no additional information compared to the absolute MxA values after injection alone (figure, B and C).

Discussion. Our data confirm that measuring MxA transcription in whole blood offers a practical method for monitoring the bioactivity of all available IFNβ preparations. The method allows reliable identification of NAB<sup>high</sup> patients. Expression of MxA in NAB<sup>neg/low</sup> patients was significantly higher than in untreated controls and NAB<sup>high</sup> patients. A time window between 12 to 24 hours proved to be practical for clinical routine purposes, although a higher induction was seen after 12 hours. MxA induction in NAB<sup>low</sup> patients demonstrated sustained bioactivity. While other studies used the Kawade<sup>6</sup> method, we applied a simplified NAB CPE assay with results reported in neutralizing capacity. Nevertheless, our results are in full agreement with a recent study<sup>5</sup> clearly demonstrating a decrease of bioactivity in patients with NC above 80%. Thus, in contrast to measuring NAB levels, measuring MxA levels is a straightforward, easy to standardize tool for rating in vivo effects of IFNβ therapy.

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Supported by Deutsche Forschungsgemeinschaft (DFG, SFB 571), Biogen-Idee and Therapieforschung für Multiple Sklerose Kranke e.V.

Disclosure: R.H. and E.M. have received grant support and consultancy fees from Schering, Teva, Serono, and Biogen-Idec. The other authors report no conflicts of interest.

Received August 11, 2006. Accepted in final form November 27, 2006.

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References

Adrenoleukodystrophy-adrenomyeloneuropathy (ALD-AMN) is an X-linked disorder of the peroxisomal beta oxidation characterized by the accumulation of saturated very long chain fatty acids (VLCFA) predominantly in adrenal cortex and central as well as peripheral myelin.1 ALD-AMN is caused by mutations of the ABCD1 gene, a member of the ATP-binding cassette (ABC) transporter superfamily, and more than 400 pathogenic ABCD1 mutations have been described (www.x-ald.nl).12–14

The incidence of ALD-AMN is estimated to be between 1:20,000 and 1:100,000. Affected men may present with childhood cerebral ALD, adult-onset AMN, or Addison disease only.1,3,4 Approximately 20% of heterozygous women develop mild AMN with a mean onset age around 40 years.1 Childhood onset, cognitive decline, visual disturbances, or adrenal dysfunction are exceptional.

Herein, we describe two female ALD-AMN heterozygotes presenting with particular cerebral phenotypes, thereby expanding the clinical spectrum of female ALD-AMN and demonstrating a substantial intrafamilial variability.

Case reports. Case 1. This patient was diagnosed with manic-hebephrenic disorder at age 8 years, and had recurrent psychotic episodes thereafter. At age 25 years, neurologic examination revealed spastic paraparesis. Twenty years later, neurologic examination documented moderate cognitive deficits, severe spastic paraparesis, and a cerebellar syndrome with unsteady smooth pursuit gaze movements, dysarthria, and intention tremor. Cerebral MRI showed moderate cerebellar atrophy and pronounced T2 hyperintensities of the cerebellar white matter, but no supratentorial atrophy or signal alterations. In the following years, her condition gradually worsened and she died at age 51 years due to pneumonia.

Autopsy revealed severe demyelination in the cerebral and, considerably more pronounced, the cerebellar white matter (figure). Histologically, cerebellar lesions were gliotic and depleted of axons and oligodendroglia (figure, A, C, E, and G). Cerebral lesions presented with clusters of foamy macrophages harboring myelin and reactive, often gemistocytic astrocytes (figure, B, D, F, and H). While adrenal glands macroscopically appeared normal, histologic examination revealed numerous adrenocortical cells with lamellar eosinophilic cytoplasmic inclusions (figure, I and J).

Her brother was diagnosed with Addison disease at age 47 years. He developed progressive spastic paraparesis and polyneuropathy in his sixth decade. Electroneuromyography showed demyelinating polyneuropathy. Cognitive testing and cerebral MRI were normal.

Case 2. At age 35 years, 1 year after her son died from ALD, this patient became unable to run. Walking difficulties increased and she became wheelchair-dependent at age 48 years. Seven years later, she noted progressive bilateral visual loss. Neurologic examination revealed severe spastic tetraparesis and mild polyneuropathy. Cognitive testing was normal. Ophthalmologic examination demonstrated reduced visual acuity (20/40 in the right eye, 20/30 in the left), severe diffuse visual field impairment, and bilateral optic atrophy (OA). Visually evoked potentials demonstrated bilaterally prolonged P100 latencies (142 msec in the right eye, 135 msec in the left, normal <118 msec). Cerebral MRI revealed bilateral parieto-occipital T2 hyperintensities (not shown).

Molecular genetic analysis. DNA was extracted from paraffin-embedded tissue (Patient 1) or from whole blood (Patient 2). The 10 exons of the ABCD1 gene were amplified, mutation screening was performed with single stranded DNA conformation sensitive (SSCP) electrophoresis, and exons with abnormal SSCP conformers were sequenced. In the brother of Patient 1, a point mutation in exon 7 was found (c.1772G>A), predicting replacement of arginine by glutamine (p.R591Q). Direct sequencing confirmed heterozygosity in Patient 1. In Patient 2, a heterozygous point mutation in exon 2 was found (c.1039C>G), predicting replacement of proline by arginine (p.P218R).

The methylation pattern at the androgen receptor (AR) locus was examined as previously described with minor modifications.2 In Patient 1, moderately skewed patterns with values of 65:35 (liver) and 82:18 (kidney) were seen. Patient 2 demonstrated a highly skewed X-inactivation with a ratio of 96:4.

Discussion. Both patients had adult-onset AMN, confirming that spastic paraparesis represents the core feature in female ALD-AMN. However, our observations emphasize a possibly earlier onset and broader phenotypic spectrum. The first patient had a childhood-onset psychiatric disorder and adult-onset olivoponto-cerebellar syndrome due to predominant cerebellar involvement. Similar manifestations are known in male ALD-AMN, but are exceptional in manifesting heterozygous women.1,2,3 The second patient had late-onset optic atrophy, which has formerly been described only in male childhood-onset ALD. Since the brother of the first patient had Addison disease and late-onset AMN, our observations also document a remarkable intrafamilial phenotypic variability.

Highly skewed X-inactivation was observed in one third of symptomatic female ALD-AMN patients but not in asymptomatic mutation carriers.4,7 Skewing of X-inactivation was therefore proposed to correlate with clinical severity in ALD-AMN carriers.4 We found a significantly skewed X-inactivation in the second patient, whereas the first patient had only moderately skewing in liver and kidney tissue. Although the sample origin might influence the degree of X-inactivation, additional genetic or environmental factors have to be postulated to explain the phenotypic variability of female ALD-AMN.

Our observations illustrate and broaden the phenotypic spectrum of manifesting female ALD-AMN carriers and underline the importance to consider female ALD-AMN in the differential diagnosis of various neurologic disorders.
Figure. Brain autopsy: coronal sections of the cerebellum (A) and the cerebrum (B) of Patient 1 depict sharply demarcated white matter lesions. Areas in A and B indicate the corresponding microscopic regions. White matter lesions in the cerebellum were extensive, partially microcystic, did not affect the molecular and granular cell layers (ml and gcl; hematoxylin and eosin, HE; C), and were strongly gliotic as demonstrated by positivity for glial fibrillary acidic protein (GFAP; E). Only few residual CD68+ macrophages remained in these lesions (G). Cerebral lesions located in the basal ganglia presented with rather fresh and CD68+ foamy macrophage-rich lesions restricted to the white matter (HE, D; Luxol-Nissl, LN, F; CD68, H). Foamy macrophages presented as myelinophages harboring myelin (insert in F, spotted blue material inside foamy macrophages). Adrenal gland: Microscopic appearance of Patient’s one adrenal gland revealed striated adrenocortical cells (I) containing lamellar eosinophilic cytoplasmic inclusions (arrows in J); while ballooned cells were not visible (HE, I and J). Scale bars: A and B: 1 cm; C: 1 mm; D through I: 200 μm; insert in F and J: 20 μm.
Myosin storage myopathy (MSM) associated with mutations in MYH7 encoding for slow/β-cardiac myosin heavy chain (MyHC), occurs sporadically or shows autosomal dominant inheritance.1-4 MSM is usually associated with severe skeletal muscle weakness, but cardiomyopathy is typically not present. We describe a patient with MSM in whom there was a homozygous mutation (Glu1,883Lys) in MYH7. The parents were second cousins, and three of their children developed progressive MSM with respiratory muscle weakness and hypertrophic cardiomyopathy. Case 3.

Muscle samples from the three siblings-three of whom were affected; the parents were second cousins. There was no family history of muscle weakness. The father died at age 58 and the mother with myocardial infarction at age 70.

Case 1. Exertional dyspnea commenced in late adolescence for this patient. She presented at age 26 in heart failure, with elevated jugular venous pressure (8 cm), soft systolic murmur at the left sternal edge, and fourth heart sound. She was short (height 141 cm), with thoracic scoliosis. Lung function tests revealed a restrictive deficit. EKG showed right bundle branch block, right axis deviation, and sinus tachycardia. Echocardiography and cardiac catheterization revealed hypertrophic, nonobstructive cardiomyopathy with elevated right ventricular pressure (40 mm Hg systolic) and a restrictive right and left ventricular pattern. Five years later, she developed an acute suppurative cervical lymphadenitis. Examination at age 34 revealed symmetric limb-girdle weakness and wasting, with mild calf hypertrophy, without myotonia. The blood creatine kinase (CK) level was 161 IU/L (normal < 50 IU/L). Electromyography revealed myopathic motor units. A deltoid muscle biopsy was taken. Her muscle weakness progressed, and by age 45 she was wheelchair dependent. She developed hypoplastic respiratory and cardiac failure requiring nocturnal volume-cycled nasal ventilatory support, with antihistamine and diuretic therapy. She died at age 57 in cardiorespiratory failure.

Case 2. The younger brother of Case 1 presented at age 25 in acute pulmonary edema following general anesthesia after a traumatic fracture. There was a history of daytime somnolence and headache, with exertional dyspnea. Examination revealed short stature (height 155 cm), with a myopathic facies, a high-arched palate, thoracic scoliosis, a weak sniff test, and proximal weakness and wasting. The CK level was 201 IU/L (normal < 160 IU/L). Investigation revealed biventricular hypertrophic cardiomyopathy. He died at age 32 from cardiac failure.

Case 3. This brother presented at age 44 with daytime somnolence, leg weakness, and hypoplastic respiratory failure, requiring urgent tracheostomy and ventilatory support. He was of short stature (height 155 cm), with a myopathic facies, a high-arched palate, thoracic scoliosis, a weak sniff test, and proximal muscle weakness and wasting, but no myotonia. The CK level was >3,000 IU/L (normal < 160 IU/L). Investigation revealed biventricular hypertrophic cardiomyopathy and heart failure. He was managed with nasal positive pressure ventilation and diuretic therapy. A biceps brachii muscle biopsy was performed.

Muscle biopsy findings. Muscle samples from the three siblings showed similar findings typical for MSM. Hyaline bodies were seen in type I fibers, but not in type II fibers, consisting of amorphous eosinophilic material, faintly green in Gomori trichrome, negative in oxidative enzyme preparations and periodic acid–Schiff, but faintly positive in ATPase preincubated at pH 4.3. Immunohistochemistry for titin, nebulin, and myomesin was negative. Electron microscopy revealed moderately electron-dense, nonfilamentous, finely granular amorphous material that seemed to infiltrate myofibrils. Cardiac muscle from Case 2 at autopsy showed fibrosis, loss of myocytes, and hyaline bodies in remaining myocytes.

Genetic findings. The entire coding sequence of MYH7 in genomic DNA was sequenced in Case 3. We identified a homozygous mutation in exon 38 (Glu1,899→Asp) (figure E-1), changing the highly conserved and negatively charged glutamate at position 1,883 to the positively charged lysine (figure E-1 on the Neurology Web site [www.neurology.org]). The Glu1,883Lys mutation is located in the distal end of the filament forming rod region of slow/β-cardiac MyHC, in the 29-residue assembly-competence domain (1,871 to 1,899), which is essential for filament assembly (figure E-1).

Accession numbers were for genomic MYH7 sequence aj238393 and for cDNA MYH7 sequence m58018.

Discussion. This family with MSM presented with type II respiratory failure and cardiac failure, due to hypertrophic cardiomyopathy, associated with a homozygous mutation in the distal rod region of slow/β-cardiac MyHC. The mode of inheritance differs from previously described patients with MSM and MYH7 mutations. The parents were unaffected second cousins. The investigated sibling was homozygous for the mutation, suggesting autosomal recessive inheritance. The previously reported cases with MSM associated with MYH7 mutations were heterozygous for the mutation, and dominant inheritance was demonstrated for these mutations. Previously reported patients with dominantly inherited MSM associated with MYH7 mutations have not developed cardiomyopathy or type II respiratory failure, suggesting that the phenotypes of recessively and dominantly inherited cases differ. The majority of MYH7 mutations are dominant and associated with cardiomyopathy, but there are reported examples of mutations in MYH7, without skeletal myopathy, causing severe cardiomyopathy in myohyozoites but only mild or no signs of cardiomyopathy in heterozygotes. In the family with MSM reported here, genetic analysis could only be performed in Case 3, and therefore we cannot rule out heterozygosity in the other siblings. Although previously reported patients with MSM associated with different MYH7 mutations did not show cardiomyopathy, this is not unique, as in Laing early-onset distal myopathy,1-3 mutations in another region of MYH7, cardiac involvement is absent.

As in previously reported patients with MSM, the mutated residue is located in a b-, f-, or c-position in the coiled-coil structure of the distal rod domain of the MyHC dimer (figure E-1). Residues in these positions may interact with other MyHC dimers or myosin binding proteins, explaining why mutations affecting such residues can cause defective assembly of thick filaments. The previously reported cases were all heterozygous for the mutation, whereas our Case 3 was homozygous. The parents were second cousins and therefore probably unaffected heterozygous carriers of the mutation, indicating that the Glu1,883Lys mutation is less pathogenic in recessive form than the previously reported MYH7 mutations associated with MSM. Our findings suggest that the mutated residue Glu1,883, which is located within the assembly-competence domain of the MyHC, is important for thick filament assembly both in skeletal and in cardiac muscle.

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Supported by grants from the Swedish Research Council (project no. 07122) and the Association Française Contre les Myopathies.

Disclosure: The authors report no conflicts of interest.

Received August 31, 2006. Accepted in final form November 30, 2006.

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