Clinical/Scientific Notes

Aamir Badruddin, MD
Ravi S. Menon, MD
Anthony T. Reder, MD

4-AMINOPYRIDINE TOXICITY MIMICS AUTOIMMUNE-MEDIATED LIMBIC ENCEPHALITIS

4-Aminopyridine (4-AP) is a potassium channel blocker which increases motor performance and walking speed in multiple sclerosis (MS) and spinal cord injury.[1] It enhances action potentials by blocking open potassium channels. 4-AP toxicity can cause dizziness, nausea, weakness, psychosis, and seizures.[2]

In limbic encephalitis, antibodies bind voltage-gated potassium channels (VGKC) and damage peripheral and central neurons.[3] VGKC subtypes exist in brain, peripheral nerves, vascular endothelium, and all muscle types.[4] We document that severe 4-AP overdose causes significant abulia, cognitive impairment, and prominent myopathic changes in heart and skeletal muscle. The temporal lobe MRI signal and clinical presentation have parallels to the seemingly distinct disease, limbic encephalitis.

Case report. A 22-year-old man with MS ingested 30 10-mg tablets of 4-AP. He had agitated behavior but was oriented, conversant, and without focal neurologic deficits or muscle fibrillations. He had cool, flushed, diaphoretic skin with temperature of 38.9°C. Blood pressure was 209/108 mm Hg, with runs of supraventricular tachycardia to 170 beats per minute. Intubation for airway protection led to intensive care unit admission.

EEG exhibited frequent diffuse polyspike and spike-wave discharges that normalized over time. There were no electrographic or clinical seizures. Transthoracic echocardiogram revealed diffuse hypokinesis, and an ejection fraction of 24%. CSF fluid on admission and 4 days after overdose had normal cell count, protein, and glucose, but contained CSF oligoclonal bands. Bilateral medial temporal lobe MRI hyperintensity (figure) on T2 and fluid-attenuated inversion recovery did not enhance with gadolinium. His MRI before overdose did not show these signal abnormalities.

Five days after overdose, he was awake with spontaneous eye opening, but had minimal awareness of the examiner and did not speak. He displayed minimal bradykinetic movement to noxious stimuli, and had symmetric 1/5 strength on Ashworth scale. By the ninth day, serum CPK peaked at 494 IU/L. He produced rare, hypophonic, lucid speech and followed simple commands. Neuropsychiatric evaluation revealed profound memory loss.

A right ventricular endomyocardial biopsy excluded inflammation, fibrosis, or toxic inclusions on day 12. The ejection fraction normalized (57%). Nerve conduction velocities were normal. EMG demonstrated myopathy in multiple myotomes. Muscle biopsy showed mild focal endomysial inflammation, with normal blood vessels and muscle architecture.

At 27 days the patient's affect was brighter, with rare, hypophonic speech; he had 3/5 antigravity limb movement. Over the next 8 weeks, his speech and language returned to normal and he walked independently. Despite 3 months of cognitive rehabilitation, he had significant anterograde and retrograde memory dysfunction and inefficient cognitive processing, suggesting medial temporal lobe dysfunction. MRI signal abnormalities were no longer present at 4 months.

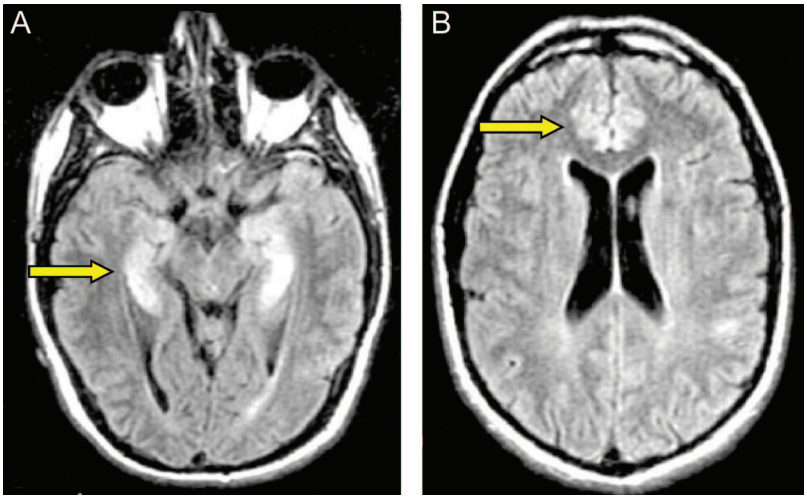
One year after 4-AP overdose, spontaneous speech, motor and verbal responses, strength, balance, and gait had improved to baseline status. He had difficulty with short-term memory and learning new tasks.

Discussion. The cognitive deficits, abulia, and temporal lobe lesions on MRI are strikingly similar to findings in patients with HSV or paraneoplastic limbic encephalitis.[5] Clinical and radiographic findings likely resulted from direct high-dose 4-AP toxicity to CNS neurons and cardiac and skeletal muscle.

An infectious etiology is unlikely. Two CSF studies showed no lymphocytosis; CSF PCR for HSV and viral cultures were negative. Paraneoplastic disease is unlikely because of the acute onset and lack of progression. Morvan disease is unlikely in the absence of neuromyotonia and insidious clinical course, vs the acute onset in this patient.[6]

VGKC are present in brain and peripheral nerves.[6] There are antibodies to VGKC in neuromyotonia, a PNS disease, as well as in Morvan syndrome, which involves CNS, peripheral nervous system, and autonomic nerves. VGKC blockage reduces glucose metabolism in the hippocampus and

Figure Sagittal fluid-attenuated inversion recovery MRI demonstrating increased signal intensity in (A) both medial temporal lobes and (B) anterior cingulum



Papez circuit, affecting memory and learning.[7] In Morvan syndrome and limbic encephalitis, antibodies to Kv 1.1, 1.2, and 1.6 in the molecular layer of the dentate gyrus are associated with memory disruption and agitation.[5] Blockade of Kv1.1 and other Kv1 subtypes, concentrated in the hippocampus and limbic circuit, is likely in 4-AP-induced limbic encephalitis, and it could explain amnesia, bradykinesia, and impaired visual learning.

Kv1.5 VGKC are present in skeletal muscles and the heart. 4-AP toxicity causes supraventricular tachycardias and atrial fibrillation.[2] Here, supraventricular tachycardia and severe contractile dysfunction resolved with time. The cardiac dysfunction, clinical weakness, EMG abnormalities, and skeletal muscle findings reflect a reversible toxic myopathy from direct 4-AP toxicity, as there was no history of prolonged muscle disuse or exertion.

Clinical improvement as 4-AP was metabolized suggests that early removal of antibodies to K+ channels could also reverse deficits in autoimmune limbic encephalitis. The similarity between antibody-mediated limbic encephalitis and pharmacologically induced encephalitis suggests that an animal model for reversible limbic encephalitis could be developed using pharmacologic blockade of VGKC.

From the Department of Neurology, University of Chicago Medical Center, IL.

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Address correspondence and reprint requests to Dr. Anthony Reder, The University of Chicago, Department of Neurology MC-2030, 5841 S. Maryland Ave, Chicago, IL 60637; areder@neurology.bsd.uchicago.edu

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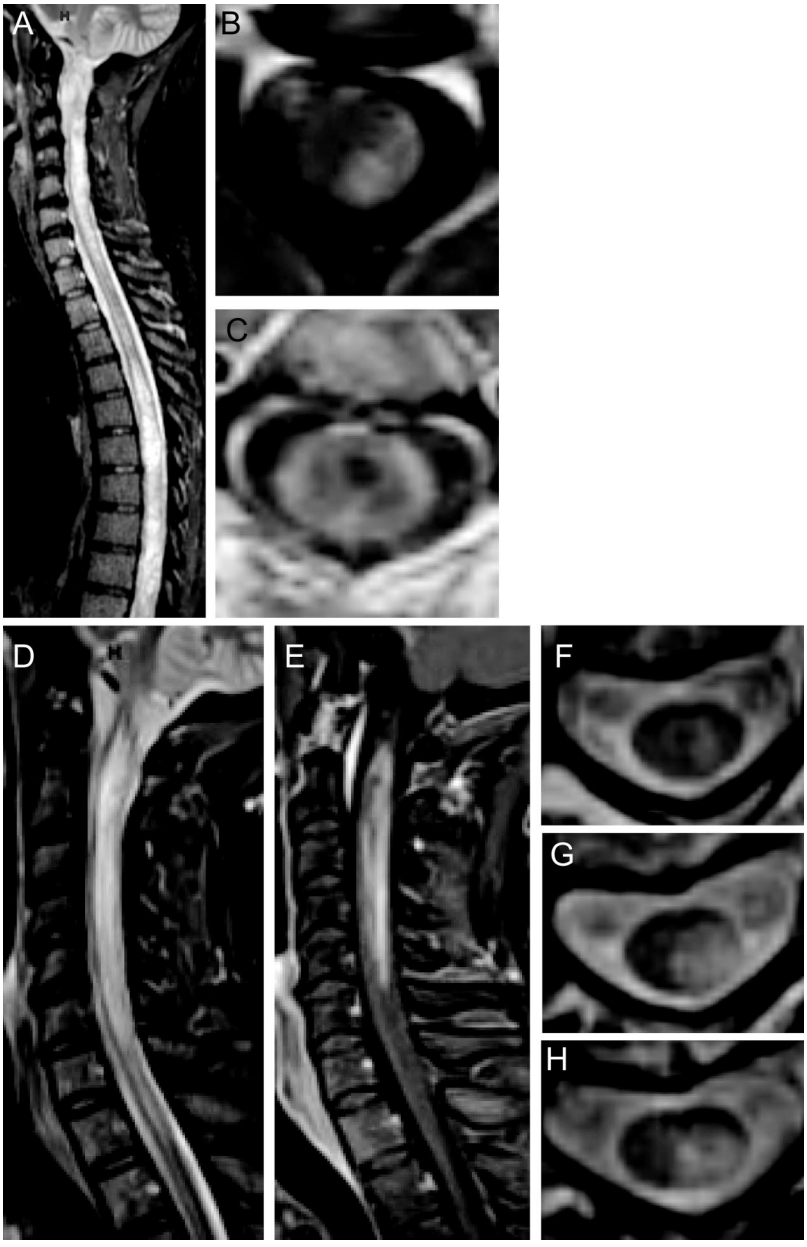
E.C. Klawiter, MD
E. Alvarez III, MD, PhD
J. Xu, PhD
A.R. Paciorkowski, MD
L. Zhu, MD, PhD
B.J. Parks, MD
A.H. Cross, MD
R.T. Naismith, MD

NMO-IgG DETECTED IN CSF IN SERONEGATIVE NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO) is an inflammatory and demyelinating disease characterized by recurrent attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM).[1] NMO is associated with antibodies against the aquaporin-4 (AQP4) water channel.[2] NMO–immunoglobulin G (IgG) predicts a relapsing course and is a supportive criterion for NMO.[3-5] The high risk of relapse, sometimes with devastating effects, makes early diagnosis important. Early identification permits counseling and consideration for immunosuppressive therapy. The serum NMO-IgG assay, using indirect immunofluorescence, is 73% sensitive and 91% specific for clinically defined NMO.[6] While helpful when positive, the sensitivity is insufficient to exclude the diagnosis. We describe 3 of 26 patients with NMO at our institution with NMO-IgG positivity restricted to CSF.

Case reports. ***Case 1.*** A 25-year-old African American woman presented with leg numbness and mild tetraparesis that resolved over 1 month. Two months later, she developed a midthoracic sensory level, again with recovery. The next month, bilateral leg weakness impaired her ability to ambulate. MRI (figure, A–C) demonstrated T2 hyperintensi-

Figure Neuroimaging of CSF antibody-positive neuromyelitis optica



Case 1: Sagittal T2-weighted STIR MRI (A) shows hyperintensity throughout the cervical and thoracic spinal cord. Axial T1-weighted postgadolinium MRI at the level C2 (B) shows dorsal enhancement and at level C2–3 (C) shows peripheral enhancement and a central T1-weighted hypointensity. Case 2: Sagittal T2-weighted STIR MRI (D) shows hyperintensity from the lower medulla caudally with enhancement on T1-weighted postgadolinium MRI (E). Case 3: Axial T2-weighted MRI at successive levels C2 (F), C3 (G), and C4 (H) show central gray matter involvement.

ties (T2H) and patchy enhancement spanning the medulla through C7 and T2–T11. Brain MRI revealed a single nonspecific T2H. Visual evoked potentials (VEPs) were normal. Serum NMO-IgG was negative but CSF NMO-IgG was positive. IgG index was elevated to 0.79, CSF leukocytes were 24/μL, but albumin index, IgG synthesis, and oligoclonal bands (OCBs) were normal. Serum antinuclear antibodies (ANA) were negative. Treatment included IV glucocorticoids and rituximab with no further exacerbations. After 8 months of disease, Expanded Disability Status Scale (EDSS) was 6.0.

Case 2. A 43 year-old African American woman presented with right-sided weakness and numbness. MRI demonstrated longitudinally extensive T2H with enhancement from the lower medulla through C6. Brain MRI was nondiagnostic. Serum NMO-IgG was negative. She recovered after IV glucocorticoids. Four months later, she developed right-sided weakness, left-sided numbness, and difficulty ambulating. Cervical spine MRI (figure, D and E) showed increased T2H with enhancement. VEPs were normal. Repeat serum NMO-IgG was negative. CSF NMO-IgG was positive with 1:8 titer. CSF IgG index was 0.76, IgG synthesis rate was 6.5, with 6 leukocytes/μL. OCBs and albumin index were normal. Serum ANA was negative. Treatment has included monthly IV glucocorticoids with no exacerbations. EDSS after 5 months of disease was 2.0.

Case 3. A 49-year-old white woman presented with left upper extremity paresthesias and clumsiness. This improved, but was followed 2 months later by ascending bilateral numbness and weakness requiring a walker. MRI (figure, F–H) demonstrated enhancing expansile T2 hyperintensity spanning C2–C5. Brain MRI and VEPs were normal. She improved with IV glucocorticoids. NMO-IgG was negative in serum, but positive in CSF. Other CSF parameters were normal. Serum ANA was 1:320. Azathioprine was started, with no further exacerbations. After 2 years of disease, EDSS was 2.0.

Discussion. We report three cases of NMO spectrum disorder with restriction of NMO-IgG positivity to the CSF. The cases presented with rapidly relapsing LETM, and a normal or nondiagnostic brain MRI. While none showed evidence for ON, these individuals have been followed less than 2 years. In each case, the second relapse was severe and disabling, occurring within months of onset. In each patient, serum NMO-IgG testing was negative at a 1:120 dilution and simultaneous CSF NMO-IgG was positive during an exacerbation, before administration of corticosteroids. Antibody testing was performed by the same laboratory (Mayo Medical Laboratories). The cause of NMO-IgG seronegativity in these three CSF-positive patients is unknown. The presence of a coexisting, interfering antibody may hinder serologic interpretation. However, only case 3 was noted to have coexisting ANA. The CSF albumin indices indicated intact blood–brain barriers.

Serum testing for NMO-IgG remains the standard test for confirming a diagnosis of relapsing NMO spectrum disorder. In our three seronegative cases of relapsing LETM, detection of NMO-IgG in the CSF confirmed the diagnosis of an NMO spectrum disorder, and mandated initiation of immunosuppressive therapies. The potential value of early treatment emphasizes the importance of making the correct diagnosis.[7] If NMO is strongly suspected and serum NMO-IgG is negative, measurement of CSF NMO-IgG is recommended and may add to the overall sensitivity of laboratory testing. Clinical scenarios that may warrant supplementary testing of CSF include the following: 1) LETM, 2) relapsing TM, 3) severe and bilateral ON, 4) ON with poor recovery, and 5) rapidly relapsing ON.

CSF studies should not be a substitute for serum testing. Larger systematic studies are required to determine the sensitivity and specificity of combined serum and CSF testing. Whether distinct clinical characteristics exist for cases with CSF restricted NMO-IgG positivity remains to be determined.

From Washington University, St. Louis, MO.

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Address correspondence and reprint requests to Dr. Eric Klawiter, Neurology, Box 8111, 660 S. Euclid Ave., Washington University, St. Louis, MO 63110; klawitere@neuro.wustl.edu

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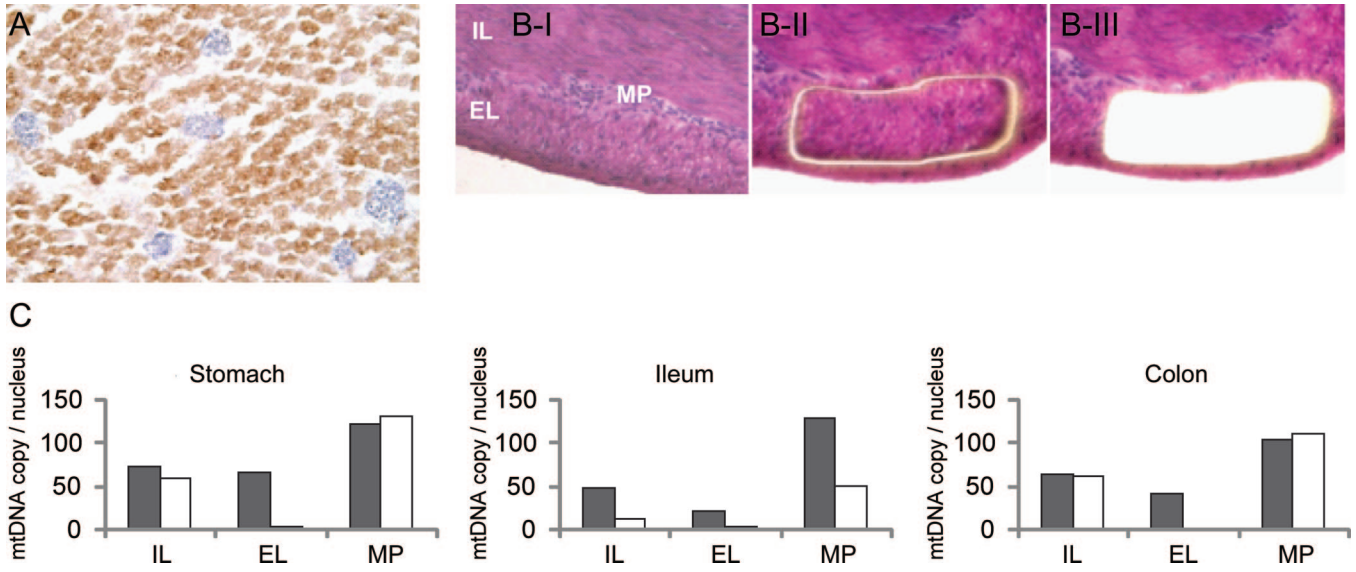
C. Giordano, MD, PhD
H. Powell, BSc
M. Leopizzi, BSc
M. de Curtis, MD
C. Travaglini, BSc
M. Sebastiani, PhD
P. Gallo, MD
R.W. Taylor, PhD
G. d'Amati, MD, PhD

FATAL CONGENITAL MYOPATHY AND GASTROINTESTINAL PSEUDO-OBSTRUCTION DUE TO *POLG1* MUTATIONS

Mutations in the gene coding for the catalytic subunit of the mitochondrial DNA (mtDNA) polymerase γ (*POLG1*) are associated with a range of clinical syndromes characterized by secondary mtDNA defects, including mtDNA depletion and multiple mtDNA deletions.[1] The phenotypic spectrum of *POLG1*-associated disease ranges from fatal childhood encephalopathy with intractable epilepsy and liver failure (Alpers-Huttenlocher syndrome)[2] to late-onset clinical disease affecting a single organ (for a review, see reference 3). We describe a fatal skeletal and visceral myopathy in the neonatal period associated with recessive *POLG1* mutations.

Case report. A newborn boy of healthy nonconsanguineous parents was delivered at 37 weeks' gestation by cesarean section. His mother (primipara, 32 years old) had been admitted to our hospital 2 weeks previously because of reduced fetal intrauterine movements and polyhydramnios. The child's birthweight was 2,330 g (<10th percentile), length 47 cm, and head circumference 33.2 cm (25th percentile). He had low-set ears and bilateral clubfoot. Apgar scores were 2, 6, and 7 at 1, 5, and 10 minutes. The child presented with severe hypotonia and generalized

Figure Morpho-molecular features of skeletal muscle and gastrointestinal tract



(A) Combined COX/SDH histochemistry on skeletal muscle biopsy showing numerous hypertrophic COX-deficient muscle fibers (blue). (B) Small intestine wall of *POLG1* patient, before (I), during (II), and after (III) laser microdissection of cells from the external layer of muscularis propria. Histologic features are unremarkable. Hematoxylin-eosin, x20. (C) Real-time PCR evaluation of mtDNA amount on microdissected tissue from gastrointestinal wall of patient (white) and one age-matched autopsy control (gray). Data are expressed as the mean value of three repeated measurements. MP = myenteric plexus; IL = internal layer; EL = external layer of muscularis propria.

muscle weakness, requiring ventilatory assistance and total parenteral nutrition. Weaning failed because of inadequate pulmonary ventilation and respiratory acidosis. Hearing loss was detected by auditory evoked potentials, while cranial MRI showed mildly enlarged ventricles and liquor spaces. Two days after birth, the infant presented with severe abdominal distension with a hypoactive bowel. MRI revealed marked intestinal dilation without mechanical obstruction. Laboratory investigations showed hypoglycemia (27 mg/dL), hypomagnesemia (0.58 mmol/L), and hypokalemia (2.4 mmol/L). Blood lactate was normal (1.3 mmol/L, normal range 0.5–2.2 mmol/L) and liver enzymes were unremarkable. A skeletal muscle biopsy was performed and showed scattered, hypertrophic cytochrome *c* oxidase (COX)-deficient and succinate dehydrogenase–positive muscle fibers (figure), suggesting a mitochondrial disorder. Molecular genetic studies revealed marked mtDNA depletion in muscle (93% decrease as compared to age-matched controls), while a screen for mtDNA rearrangements within individual COX-positive and COX-deficient fibers[4] was negative. We sequenced the entire coding region and intron-exon boundaries of the *POLG1* gene, identifying two reported heterozygous missense mutations in compound c.679C>T predicting p.R227W and c.2542G>A predicting p.G848S. Sequencing of parental samples confirmed recessive inheritance.

Supplemental data at www.neurology.org

The infant died at 20 days of respiratory failure. At autopsy, the brain did not show remarkable changes on gross examination. Histology was not informative due to poor preservation of tissue; there was no evidence of neuronal damage in the spinal cord. The liver showed diffuse cholestasis, consistent with total parenteral nutrition; hepatocyte steatosis, necrosis, or liver fibrosis were not observed. The testicles were undescended, while remaining visceral organs were normal except for a marked dilation and thinning of the bowel wall. Despite normal histology, analysis of stomach, ileum, and colon homogenates revealed severe mtDNA depletion (up to 94% decrease; table e-1 on the *Neurology*® Web site at www.neurology.org). Laser capture microdissection analysis[5] revealed that the mtDNA depletion was confined to the muscularis propria, being most prominent in its external layer (figure). Ganglion cells from the myenteric plexus showed milder mtDNA depletion, restricted to the small intestine (figure). There was no mtDNA depletion in liver (not shown).

Discussion. We describe an infant with a multisystem disorder whose main clinical features were severe skeletal myopathy and visceral dysmotility. Sequencing of the *POLG1* gene identified compound heterozygous mutations. Both mutations have been reported previously as recessive, although not together; the p.G848S mutation in patients presenting with PEO, Alpers-Huttenlocher syndrome, and a case with encephalopathy and stroke-like episodes; the p.R227W mutation in Alpers-Huttenlocher syndrome and sporadic PEO (http://tools.niehs.nih.gov/polg).

Children with mutations in *POLG1* typically manifest in the first years of life with Alpers-Huttenlocher syndrome[2] or a progressive multisystem disorder without liver failure. Combined respiratory chain deficiency due to mtDNA depletion in affected tissues is often observed.[3,6] Our patient showed mild cerebral atrophy, yet typical symptoms of Alpers-Huttenlocher syndrome such as intractable seizures and signs of liver dysfunction were not observed. The prominent feature was a severe muscle weakness, with marked mtDNA depletion and COX-deficient muscle fibers, leading to death from respiratory insufficiency. In addition, mtDNA depletion was the likely cause of a visceral myopathy causing hypoperistalsis and intestinal pseudo-obstruction. The molecular features observed in the gastrointestinal tract parallel those recently reported in another autosomal recessive syndrome, mitochondrial neurogastrointestinal encephalomyopathy.[5] Based on these findings, the external layer of muscularis propria is confirmed as the most susceptible point of the gastrointestinal tract to develop mtDNA depletion, possibly because of the constitutive low abundance of mtDNA within smooth muscle cells at this site.

From the Dipartimento di Medicina Sperimentale (C.G., M.L., C.T., M.S., P.G., G.d.) and Dipartimento di Ginecologia, Perinatologia e Puericultura (M.d.C.), Sapienza, Università di Roma, Rome, Italy; Northern Regional Genetics Service (H.P.), Institute of Human Genetics, Newcastle upon Tyne; and Mitochondrial Research Group (R.W.T.), Newcastle University, Newcastle upon Tyne, UK.

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Address correspondence and reprint requests to Dr. Giulia d'Amati, Department of Experimental Pathology, Sect. of Pathology, Sapienza University, Policlinico Umberto I, Viale Regina Elena 324, 00161 Rome, Italy; giulia.damati@uniroma1.it

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