Hereditary Neuronal Intranuclear Inclusion Disease With Autonomic Failure and Cerebellar Degeneration

Raffaella Zannolli, MD; Sid Gilman, MD, FRCP; Simone Rossi, MD; Nila Volpi, MD; Andrea Bernini, MD; Paolo Galluzzi, MD; Daniela Galimberti, MD; Lucia Pucci, PhD; Alfonso D’Ambrosio, MD; Guido Morgese, MD; Fabio Giannini, MD

Background: Neuronal intranuclear inclusion disease (NIID), a multiple-system degeneration, occurs usually as a sporadic disorder with onset in childhood. The disease has been found in monozygotic twins and in siblings. In 2 previously described families, the disorder has affected 2 generations.

Objective: To investigate the clinical, anatomical, and electrophysiological characteristics of NIID that affect the central nervous system and the central and peripheral components of the autonomic nervous system in 2 successive generations of a family.

Design: Case report.

Setting: Tertiary care hospital.

Patients: A 53-year old woman and her sons, aged 28 and 25 years. Symptoms began in childhood in 2 of the 3 cases, and consisted of urinary and fecal incontinence, erectile dysfunction in the men, and recurrent orthostatic hypotension.

Methods: We used results of clinical neurological evaluations; cranial magnetic resonance imaging; skeletal muscle and sphincter electromyography (EMG); peripheral nerve conduction and bulbocavernosus reflex studies; autonomic function tests; brainstem, visual, somatosensory, and motor evoked potentials; auditory and vestibular testing; metabolic and molecular genetic testing; and muscle and rectal biopsy with immunohistochemistry.

Results: We found variable degrees of ocular dysmetria in 2 cases, ataxic dysarthria and limb ataxia in 1, and hyperreflexia in 2. Magnetic resonance imaging revealed cerebellar atrophy in all 3 cases and diffuse cerebral cortical atrophy in 1. Results of peripheral nerve conduction studies were normal. Sphincter EMG findings were abnormal in 2 of the 3 cases, and results of autonomic function tests were abnormal in the same 2. The EMG in 1 case revealed a chronic neurogenic pattern in the distal limb muscles. Metabolic and molecular genetic testing revealed no abnormal findings. Results of the muscle biopsy were negative, but results of the rectal biopsy revealed eosinophilic ubiquitinated intranuclear inclusions in neurons.

Conclusion: Transmission of NIID in 2 generations presenting with autonomic failure and cerebellar ataxia was hereditary.

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PATIENTS AND METHODS

All 3 family members underwent evaluation including a his-
tory, medical and neurological examinations, and the spe-
cific diagnostic tests listed subsequently.

AUDITORY AND VESTIBULAR TESTS

The tests, previously described, included observations of
cytosism, smooth pursuit movements, saccadic move-
ments, optokinetic nystagmus, responses to caloric stimu-
ation, and pure tone audiometry.

IMAGING AND ELECTRODIAGNOSTIC STUDIES

We used cranial magnetic resonance imaging (MRI) at 0.5
and 1.5 T and included T1- and T2-weighted images in the
coronal and sagittal planes. We obtained electromyo-
grams (EMGs) of several muscles (ie, brachial biceps, first
dorsal interosseous muscle of the hand, rectus femoris, tibi-
als anterior, and orbicularis oris) to examine the shape and
size of motor unit action potentials and the interference pat-
tern. We examined the external anal sphincter (EAS) and
pubedal-nerve terminal motor latency (PNTML) using stan-
dard techniques. Using standard surface tech-
niques, we investigated sensory nerve action potentials;
conduction velocities of the median, ulnar, and sural nerves;
compound muscle action potentials; motor conduction ve-
celocities; and distal latencies in the median, ulnar, tibial,
and common peroneal nerves. We applied standard ap-
proaches to examine the median, tibial, and pudendal-
nerve somatosensory evoked potentials; the sacral bul-
bocavernous reflex; brainstem auditory evoked potentials;
and visual evoked potentials. We evaluated corticospinal
tract function with motor evoked potentials to transcran-
ial magnetic stimulation.

AUTONOMIC NERVOUS SYSTEM TESTING

We studied the sympathetic skin response (SSR) using stan-
dard methods in both hands and both feet in all 3 subjects
and in the penes of the 2 men. We obtained 3 or 4 re-
cordings of the SSR from each site (palm, sole, and penis)
and selected as representative the 2 SSRs with the clearest
reproducibility and lowest variability. The latency was ob-
tained at the first deflection and the amplitude as the base-
tline to the first peak. The SSR was considered absent if no
consistent voltage change occurred at a sensitivity of 50 µV
after 3 trials at a slightly painful intensity. We recorded the
electrocardiographic R-R interval with standard tech-
niques at rest, during deep breathing, during movement from
the lying to the standing position, and during the Valsalva
maneuver. We measured blood pressure after 2 minutes
in the recumbent position and 3 minutes after standing,
and we recorded the time course of blood pressure vari-
factions for 24 hours using standard techniques.

MUSCLE BIOPSY

We performed an open biopsy on the right vastus lateralis
muscle of patient 1.

For light microscopic examination, standard histologi-
cal and histochemical stains (hematoxylin-eosin, modified
Gomori trichrome, myofibrillar adenosine triphosphatase
[pH, 9.4], and, after acid preincubation [pH, 4.35 and 4.63],
periodic acid–Schiff, oil red O, acid phosphatase, nico-
tinamide adenine dinucleotide [reduced form]–tetrazolium re-
ductase, succinic dehydrogenase, cytochrome-c oxidase, myo-
adinitate deaminase, and phosphofructokinase) were
performed on cryostat sections 10 µm thick. Ultrathin sec-
tions from blocks routinely embedded in epoxy resin (Fluka;
Sigma-Aldrich Corp, St Louis, Mo) were also examined in
transmission electron microscopy (Philips CM10; Philips,
Eindhoven, the Netherlands).

RECTAL BIOPSY

We performed a rectal biopsy under local anesthesia on pa-
tient 1. A block was longitudinally cut, and a full-length
specimen was fixed in buffered formalin and embedded in
paraffin. Serial 8-µm-thick sections were stained with he-
matoxylin-eosin. Immunohistochemistry was performed on
9-µm-thick sections from the paraffin-embedded block fol-
lowing preestablished protocols; sections were incu-
ated overnight in a 1:1000 dilution of a polyclonal rabbit
antinubiquitin antibody (DAKO, Glostrup, Denmark) and
successively in a 1:200 dilution of goat anti–rabbit IgG
conjugated to peroxidase (Sigma-Aldrich Corp). Immuno-
 localization was revealed by means of the chromogen di-
aminobenzidine (Sigma-Aldrich Corp). Sections were
counterstained with hematoxylin. For transmission electron
microscopy, specimens were fixed in 2.5% glutaralde-
hyde–4% paraformaldehyde in cacodylate buffer and rou-
tinely processed. Immunohistochemistry slides and semi-
thin sections, after toluidine blue staining, were examined
with a light microscope (Zeiss Axiosplan; Carl Zeiss,
Oberkochen, Germany). Ultrathin sections were contrasted with
lead citrate and uranyl acetate and observed with an elec-
tron microscope (Philips CM10; Philips).

RESULTS

The Table summarizes the principal clinical features
and the results of the investigations of the 3 patients
examined.

PATIENT 1

A 28-year-old man was referred to the University of Siena,
Siena, Italy, with a long-term history of abnormally fre-
quent intestinal evacuations with more or less fluid stools
and soiling of his underclothing. In childhood, when it
started, the problem was attributed to food intolerance,
and in adolescence, to irritable bowel syndrome. At that
time, investigations revealed no food intolerance, intesti-
nal malabsorption or malabsorption, or bacterial or para-
sitic pathogens. Additional studies included blood smear;
measurement of serum electrolyte, serum urea nitrogen,
creatinine, calcium, phosphorus, albumin, and total pro-
tein levels; a search for specific nutritional deficiency (iron,
vitamin B₁₂, folic acid, and vitamin E); testing for antibod-
ies to gluten and antimyosin; and a sweat test. His pres-
cent complaints included 2 to 3 daily evacuations of loose
stools associated with mild incontinence, resulting in
chronic soiling and occasional fecal incontinence. He also complained of urinary urgency. He reported erectile dysfunction and lack of morning erections from adolescence to the present. He experienced difficulty with balance, coordination, and strength in his legs since his second decade of life. He also experienced repeated light-headedness when moving from the lying to the standing position. As a consequence of these symptoms, he stopped participating in sports as a teenager and restricted his social activities. The family history was positive for similar symptoms in his mother and his older brother. His father was asymptomatic, and there were no
other siblings in the family. On general physical examination, no abnormalities were found except for weak contraction of the EAS. Results of a neurological examination revealed normal cognitive function. Although full, extraocular movements showed overshoot dysmetria and slow pursuit movements. Speech was slow with an ataxic dysarthria. The gait was wide based and ataxic, with irregular size and directions of individual steps and difficulty turning without loss of balance. Arm and hand movements were mildly ataxic, and handwriting was consistent with ataxia. The legs were mildly weak and ataxic in attempts at coordinated movement. No parkinsonian features were detected. The deep-tendon reflexes were increased, but no clonus was found and the plantar responses were flexor.

Cranial MRI revealed atrophy of the cerebellar hemispheres (Figure 1, patient 1, A and B). The electroencephalogram revealed normal findings. An H-reflex could be recorded from the foot muscles at rest, which is an abnormal finding suggestive of subclinical corticospinal tract dysfunction. No evidence was found of a somatic peripheral neuropathy, but the EMG of the EAS revealed evidence of denervation consisting of abundant spontaneous activity at rest and a reduced interference pattern. The pudendal compound muscle action potential was reduced in amplitude despite a normal PNTML, and the bulbocavernous reflex was absent. The R-R interval variability, SSR, and results of 24-hour blood pressure monitoring were normal. Results of multimodal evoked potentials tests were also within normal limits. Cytophenetic analysis with G-banding at a 550-band resolution revealed a normal 46,XY karyotype. Results of molecular analyses for the spinocerebellar ataxia (SCA1, SCA2, SCA3, and SCA7) and the Friedreich ataxia genes were negative. Results of a muscle biopsy revealed no myopathic or neurogenic changes and no histochemical or ultrastructural evidence of a mitochondrial disease. Results of a muscle biopsy revealed sparse eosinophilic intranuclear inclusions in neurons, mainly in the myenteric plexus. Inclusions were immunoreactive to ubiquitin and consisted of fine filaments (Figure 2).

PATIENT 2

A woman aged 53 years was the mother of patients 1 and 3. She complained of recurrent syncopal episodes with momentary loss of consciousness, usually induced by moving from the lying to the standing position. These episodes began when she was about 20 years of age and had increased in frequency in recent years. She had been aware of generalized hypohidrosis for most of her adult life. She had experienced mild fecal incontinence consisting of chronic soiling and urgency of defecation for many years. She also complained of frequent urination and incomplete voiding during the same period.

Results of a general physical examination disclosed no abnormalities except for a weak EAS contrac-
Results of a neurological examination revealed normal cognition, speech, and cranial nerve functions. Extraocular movements were normal. Results of the motor system examination were also entirely normal, with no ataxia or parkinsonian features. The deep-tendon reflexes were diffusely hyperactive, but without clonus and with flexor plantar responses. Cranial MRI revealed atrophy of the cerebellar vermis and hemispheres (Figure 1, patient 2, A and B). She refused to undergo electroencephalography. The EMG showed a chronic neurogenic pattern in the distal muscles of the upper and lower limbs. Although results of motor and sensory nerve conduction studies were normal, the findings suggested a mild subclinical motor axonal peripheral neuropathy. The EMG of the EAS revealed abnormal spontaneous activity at rest (fibrillations and positive wave potentials) and a reduced interference pattern, indicating denervation. Moreover, the pudendal compound muscle action potential was reduced in amplitude, despite a normal PNTML. The SSR was abnormal, with reduced amplitude and delayed response from the sole of the right foot and absent responses from other limbs. Results of the R-R interval variability study were normal. Blood pressure monitoring for 24 hours showed continuous but asymptomatic hypotension, without variations of circadian rhythm (mean daytime systolic and diastolic blood pressure, 102.8 and 69.5 mm Hg, respectively; mean nighttime values, 100.8 and 67.0 mm Hg, respectively). During the physical examination, the blood pressure in the supine position was 105/70 mm Hg and 85/60 mm Hg 3 minutes after standing. Results of the multimodal evoked potentials tests were within normal limits. Cytogenetic analysis with G-banding at the 550-band resolution revealed a normal 46,XX karyotype.

PATIENT 3

A 25-year-old man had a history of intermittent fecal and urinary incontinence and episodic erectile failure that began sometime in adolescence. He also reported mild lightheadedness on moving from the lying to the standing position. He had noted joint laxity for many years.

Results of a general physical examination revealed marked hypotonia and joint laxity of the limbs. Results of a digital rectal examination showed weak contraction of the EAS. On neurological examination, cognitive func-

Figure 2. Rectal biopsy findings in patient 1. A and B, Ganglia cells from superficial myenteric plexus. Round intranuclear inclusions, surrounded by a thin clear halo, distinctly eosinophilic and demarcated from chromatin (arrows), are seen. A faintly visible nucleolus is seen close to the eosinophilic inclusion (asterisk) (hematoxylin-eosin, original magnification ×1000). C and D, Ubiquitin staining of inclusions (inset) diffuses to the nucleus (arrows and asterisk) (antiubiquitin immunoperoxidase, original magnification ×1000). E, Semithin section. Hyaline appearance of the inclusion (arrow) is seen, close to the nucleolus (asterisk) (toluidine blue, original magnification ×1000). F, Nuclear inclusion (arrows) consisting of intermingled fine filaments, most of which transversally sectioned, with no defined spatial array. Bar indicates 1 µm (transmission electron microscopy, original magnification ×10500).
tion was intact. Results of oculomotor testing showed overshoot dysmetria and slow pursuit movements. No abnormalities were detected in speech or in other cranial nerve functions. Examination of the motor system revealed no abnormalities, and the deep tendon reflexes were normal, with flexor plantar responses.

Cranial MRI showed subtle cerebellar hemisphere atrophy and diffuse cerebral cortical atrophy (Figure 1, patient 3, A and B). The electroencephalogram was normal. The EMG of the limb musculature showed no abnormality, and no clinical or electrophysiological evidence of a peripheral neuropathy was found. Despite the weak EAS contraction on digital examination, EMG of the EAS, amplitude of the pudendal motor response, and PNTML were normal. The bulbocavernosus reflex, however, showed a markedly delayed response (38.2 milliseconds; normal, <42.5 milliseconds). The cortical component of the pudendal somatosensory evoked potential was also markedly delayed (45.6 milliseconds; normal, <42.5 milliseconds). Results of autonomic function tests all were within normal limits, but the 24-hour blood pressure monitoring showed some asymptomatic episodes in which the blood pressure declined to 78/55 mm Hg. The multimodal evoked potentials were normal. Cytogenetic analysis with G-banding at 550-band resolution revealed a normal 46,XY karyotype.

We present, to our knowledge, the first report of 2 successive generations of a family with NIID that affected the central nervous system and the central and peripheral components of the autonomic nervous system. This report is also the second of central nervous system NIID that affected 2 successive generations of a family. In the first report, neurogenic weakness developed in female monozygotic twins in adult life, followed by cerebellar ataxia, dysarthria, and death after 20 years. An identical illness developed in 2 adult sons of 1 twin. In another family, NIID affected 2 generations with a visceral neuropathy manifested as chronic idiopathic intestinal pseudo-obstruction, and results of rectal biopsy established the diagnosis. The remaining reports of NIID concern sporadic cases except for occasional cases involving monozygotic twins and siblings.

We describe herein 3 members of a family affected by a neurological disorder involving multiple systems that began in the first or second decade of life and progressed slowly. Autonomic disorders appeared first, consisting of fecal and urinary incontinence of varying degrees, accompanied by postural hypotension and hypohidrosis in 1 case and erectile dysfunction in both male members. In 1 family member, cerebellar dysfunction affected speech, oculomotor function, and limb coordination, and structural imaging revealed widespread cerebellar atrophy. The other 2 members also had widespread cerebellar atrophy, but with only minor clinical manifestations in 1 of the 2, consisting principally of mildly abnormal extraocular movements. Hyperreflexia with normal plantar responses in 2 of the members suggested mild corticospinal involvement in addition to the autonomic and cerebellar involvement, and mild weakness of the lower extremity in patient 1 probably resulted from corticospinal disease.

Laboratory investigations confirmed the clinical impressions and added new information. The EMG of the EAS revealed a neurogenic pattern in 2 of the 3 cases, indicating denervation. Moreover, in both of these cases, the pudendal compound muscle action potential was reduced in amplitude, despite a normal PNTML. These findings indicate degeneration of the Onuf nucleus, which is located in the anterior horn of sacral segments 2, 3, and 4 and supplies the striated sphincter muscles by way of the pudendal nerves. In one son, the bulbocavernous reflex was absent, and in the second it was delayed, providing further evidence of autonomic failure and demonstrating the neurogenic basis of the erectile dysfunction.

In patient 2, who had a history of hypohidrosis, the SSR was abnormal in the limbs. The SSR serves as an index of peripheral autonomic nerve activity, especially for sudomotor function of postganglionic unmyelinated sympathetic fibers. In this same patient, the EMG revealed a chronic neurogenic pattern in the distal limb muscles, suggesting a subclinical motor axonal peripheral neuropathy. In 2 family members, hyperreflexia suggested corticospinal tract involvement, and in 1 of these (patient 1), an H-reflex could be recorded from the foot muscles at rest, providing further evidence of corticospinal involvement. Since motor evoked potentials to transcranial magnetic stimulation, which reflect the functionality of the fastest corticospinal fibers, were normal, the hyperreflexia probably resulted from dysfunction of small myelinated fibers of the corticospinal tracts.

All 3 family members complained of orthostatic light-headedness, but measurements of orthostatic changes in blood pressure revealed orthostatic hypotension only in patient 2. Moreover, 24-hour blood pressure monitoring demonstrated only asymptomatic hypotensive episodes in 2 family members.

Although no history of a similar disorder in previous generations could be ascertained, the 3 affected members of this family provide further evidence of an inherited form of NIID, possibly by means of autosomal dominant inheritance. In the previously described family with NIID of the central nervous system, the remaining reports of NIID concern sporadic cases except for occasional cases involving monozygotic twins and siblings.

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Although no history of a similar disorder in previous generations could be ascertained, the 3 affected members of this family provide further evidence of an inherited form of NIID, possibly by means of autosomal dominant inheritance. In the previously described family with NIID of the central nervous system, the previously described family with visceral NIID, only 2 generations were affected, and the transmission was considered to be autosomal dominant. The absence of similar disorders in previous generations in all 3 families suggests the possibility of a spontaneous mutation in the gene responsible for NIID. Such a mutation could also account for the previous reports of NIID affecting monozygotic twins and siblings.

Achieving a correct diagnosis of the disorder in this family proved challenging and triggered an extensive diagnostic evaluation. The rectal biopsy was the only method that allowed the correct diagnosis to be made in a living patient. The constellation of symptoms in these cases bore some similarity to a previously described multiosystem degeneration resulting from the SCA1 gene. In the patients in this previous report, a cerebellar ataxia accompanied by autonomic insufficiency, dystonia, and peripheral neuropathy developed. The onset was much later in life than in the current cases, however, and the
autonomic failure was not as severe. Moreover, results of genetic testing for the SCA1 gene (and also for the SCA2, SCA3, and SCA7 genes) were negative in the present family. This family’s disease also bears some clinical resemblance to familial amyloidotic polyneuropathy associated with cerebellar ataxia and signs of corticospinal tract dysfunction. \(^{44,45}\) This diagnosis was ruled out in the present cases by results of the peripheral nerve studies, which provided no evidence of an overt somatic polyneuropathy. Familial dysautonomia, the Riley-Day syndrome, results from a genetic disorder mapped to chromosome 9q31-q33. \(^{46,47}\) This autosomal recessive disorder affects the Ashkenazi Jewish population, causing developmental loss of neurons from the sensory and autonomic nervous system. The mode of inheritance, ethnic background, and absence of sensory abnormalities made this diagnosis unlikely in the present family. A mitochondrialdna mutation presented another possibility, in that a familial multiple-system degeneration has been reported in association with such a mutation. \(^{48}\) In the reported cases, however, parkinsonism dominated the clinical presentation, and the other disorders included dysarthria, areflexia or hyperreflexia, spasticity, ataxia, ptosis, progressive external ophthalmoplegia, and an abnormal muscle biopsy finding. Autonomic failure with urinary and fecal incontinence and postural hypotension were not found. An autosomal dominant orthostatic hypotensive disorder has been mapped to chromosome 18q. \(^{49}\) In those family members, the symptoms consisted of light-headedness on standing, which could worsen to syncope, along with palpitations and blue-purple ankle discoloration. Accompanying these symptoms, the systolic blood pressure markedly declined, the diastolic blood pressure rose, and a tachycardia developed. The symptoms did not include urinary, sexual, or fecal disorders, as in the present family.

In conclusion, the study of clinical, pathological, and electrophysiological features of NIID in a family presenting with fecal incontinence, autonomic failure, and cerebellar ataxia suggests a hereditary transmission of this condition.

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From the Department of Pediatrics, Obstetrics, and Reproductive Medicine, Section of Pediatrics (Drs Zannolli, Galimberti, Pucci, D’Ambrosio, and Morgese), Department of Surgery (Dr Bernini), and Department of Neuroscience, Section of Neurology (Drs Rossi and Giannini), Policlinico Le Scotte, and the Department of Anatomical and Biomedical Sciences (Dr Volpi), University of Siena, and the Neuroradiology Unit, Azienda Ospedaliera Senese, Policlinico Le Scotte (Dr Galluzzi), Siena, Italy; and the Department of Neurology, University of Michigan, Ann Arbor (Dr Gilman).

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Corresponding author and reprints: Raffaella Zannolli, MD, Department of Pediatrics, Obstetrics, and Reproductive Medicine, Section of Pediatrics, Policlinico Le Scotte, University of Siena, Siena, Italy (telephone: 39.0577.386143; e-mail: zannolli@unisi.it).

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