RESIDENT & FELLOW SECTION

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Pearls & Oy-sters: Niemann-Pick disease type C in a 65-year-old patient

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PEARLS

- Niemann-Pick disease type C (NPC) has heterogeneous clinical presentations.
- Although NPC usually affects infants or young adolescents, it should be considered in the differential diagnosis of vertical supranuclear gaze palsy, regardless of age at presentation.
- Adult-onset NPC may rarely present with myoclonus.
- Disease-specific therapy with miglustat has been shown to stabilize the neurologic progression in patients with NPC.

OY-STERS

- NPC can present as late as the 6th–7th decade.
- Although more common disorders like progressive supranuclear palsy (PSP) should be suspected, NPC should also be considered in the differential diagnosis of late-onset vertical gaze palsy, thereby minimizing the diagnostic delay.
- Rare symptoms of myoclonus and sensorineural hearing loss can mislead the clinician away from the diagnosis of NPC.

CASE REPORT A 65-year-old, right-handed man of Polish ancestry developed insidious onset, gradually progressive gait ataxia at the age of 55. Three years later, he started dropping things due to myoclonic jerks involving the trunk and upper extremities (video on the *Neurology*® Web site at Neurology.org). Worsening ataxia and frequent falls resulted in the use of a wheelchair by age 64. His medical history was positive for bilateral hearing loss since his early 50s. There was no history of seizures, dysphagia, mood disorders, psychosis, or any other significant medical illness in the past, besides being a 40-pack-year smoker. He was born of nonconsanguineous parents, and his sister died of an unknown illness at the age of 13. On neurologic examination, cognition was normal and speech was dysarthric. Although visual acuity was normal, there was reduced vertical gaze (more pronounced on downgaze), which responded to oculocephalic maneuver, consistent with a vertical supranuclear gaze palsy (VSGP). Horizontal eye movements were intact, and there was no nystagmus. Bilateral sensorineural hearing loss was detected, right more than left. Generalized myoclonic jerks were present, predominantly involving the upper extremities on posture maintenance. There were no features suggestive of parkinsonism. He had marked gait ataxia with milder appendicular ataxia and dysdiadochokinesia. The remainder of his neurologic examination was normal. Abdominal examination did not reveal any visceromegaly. The NPC suspicion index score[1] was 61. Laboratory workup showed normal complete blood count, serum electrolytes, creatinine, glucose, liver function test, serum lactate, and EEG. Spinocerebellar ataxia gene panel was negative for *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *SCA8*, and *SCA17*. Genetic testing for NPC was positive for 2 pathogenic variants (p.P1007A and p.1077Q) of *NPC1* gene. MRI brain showed cortical and midbrain atrophy with subcortical nonspecific white matter changes (figure). His myoclonic jerks responded to valproate 500 mg oral twice daily. He was started on miglustat 100 mg oral twice daily titrated to 200 mg oral 3 times a day.

DISCUSSION NPC is a rare lysosomal lipid storage disorder characterized by heterogeneity in the age at onset, clinical presentations, and disease course.[2] It has an incidence of 1 per 120,000 live births.[1] While mutation in the *NPC1* gene (located on chromosome 18) results in >95% of cases, mutation in the *NPC2* gene (located on chromosome 14) occurs in approximately 4% of cases.[1] The mutations cause abnormal intracellular transport and accumulation of cholesterol and glycosphingolipids in the brain and other tissues.[1,3] Based on the age at onset, patients with NPC are categorized into 5 subgroups: prenatal/perinatal (age between 0 and 3 months), early-infantile (<2 years), late-infantile (2 to <6 years), juvenile (6 to <15 years), and adolescent/adult (≥15 years).[1,3] Although previously considered a childhood-onset disorder, growing awareness along with advancements in biochemical and genetic diagnostic methods have increased detection of late-onset cases.[4] Adolescent/adult NPC cases comprised 17%–27% of the 309

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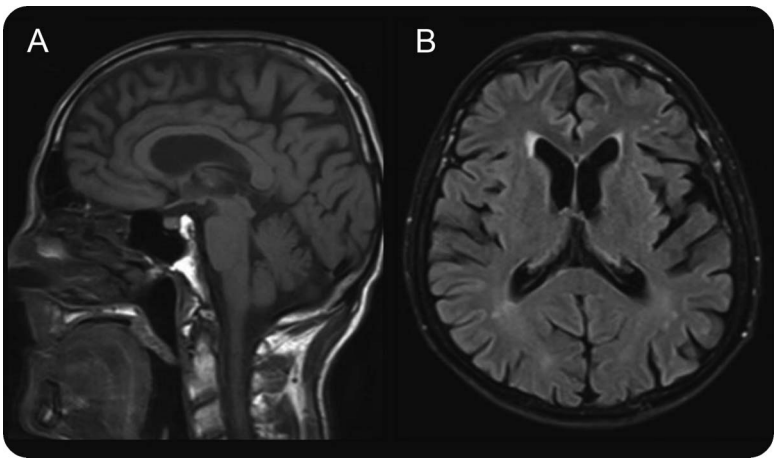
patients reported in 2 separate studies.[2,4] Of the 4 reported patients with NPC with an age >50 years at diagnosis,[5,6] 3 presented with neurologic or psychiatric manifestations.[5] Our patient had onset of neurologic symptoms at age 55 years, second only to a case reported with onset of symptoms at 59 years of age.[7]

The heterogeneous clinical manifestations of NPC include systemic, neurologic, and psychiatric features.[1] Systemic features like neonatal jaundice, hepatosplenomegaly, or isolated splenomegaly are common in early-onset disease, and always precede neurologic manifestations.[1,3] Almost 15% of all patients with NPC, and half of those with adult-onset disease, have minimal or no hepatosplenomegaly.[3] The presence of isolated splenomegaly without any hepatic derangement in patients with a neurodegenerative or psychiatric illness favors NPC.[1] The most common neurologic manifestations include cognitive or motor developmental delay in childhood-onset cases, VSGP, ataxia, dysarthria, dysphagia, dystonia, seizures, and gelastic cataplexy.[1,3] Although VSGP may be seen in other neurologic disorders (table),[8] it is one of the earliest features in NPC, and is present in 70%–80% of patients across all age at onset categories.[1,2,4] With disease progression, horizontal saccadic eye movements are also affected, leading to complete ophthalmoplegia, reflecting progressive brainstem degeneration.[1] Myoclonus is rare in adult-onset NPC,[1] but it was a major neurologic manifestation in our patient, along with VSGP, ataxia, and bilateral sensorineural hearing loss. Sensorineural hearing loss is commonly seen in clinical practice but remains underreported in patients with NPC.[1] Frontal-subcortical cognitive deficits and schizophrenia-like psychosis are usually seen in patients with adolescent/adult-onset NPC.[1,2] The combination of phenotypic and genetic heterogeneity precludes formation of genotype–phenotype correlations in patients with NPC.[4]

In order to facilitate diagnosis of NPC in suspected patients, the NPC suspicion index was developed, which incorporates visceral, neurologic, and psychiatric features, along with the family history.[1] A score ≥70 suggests immediate testing for NPC, and scores from 40 to 69 indicate a need for further follow-up.[1] The probability of NPC is very low with scores below 40.[1] Because of the NPC suspicion index score falling in the gray zone (40–69), along with the heterogeneity in clinical presentation, long diagnostic delays occur in patients with adult-onset NPC,[1–3] as seen in our patient. In the 3 reported patients with NPC with neurologic illness and age at diagnosis >50 years, the mean delay in diagnosis was 13.5 years for the 2 cases where data was available.[5] In our patient, there was a delay of almost 10 years in reaching the diagnosis of NPC. Thus, in adult patients with progressive VSGP, ataxia, dysarthria, dysphagia, cognitive decline, and psychiatric symptoms, one should suspect NPC. An accompanying family history suggestive of NPC is helpful but not necessary. The clinical diagnosis may be supported by brain imaging findings, which alone are nondiagnostic.[1,3] MRI brain may show cerebral or cerebellar atrophy, white matter hyperintensities, and midbrain atrophy,[1] as was seen in our patient. There is a lesser degree of increase in pontine-to-midbrain ratio in adult patients with NPC than that seen in PSP.[9]

Patients with NPC with onset of neurologic disease in early childhood develop rapid disease progression, and die at a younger age, as compared to those with late-onset neurologic involvement.[1,4] Progressive dysphagia leading to repeated aspirations and bronchopneumonia causes the majority of deaths in patients with NPC.[1] Symptomatic treatment for various neurologic and psychiatric manifestations improves quality of life in patients with NPC.[1] The myoclonic jerks in our patient improved on valproate. Miglustat is the only disease-specific therapy approved to treat progressive neurologic manifestations in pediatric and adult patients with NPC.[10] It competitively inhibits glucosylceramide synthase, and reduces glycosphingolipid accumulation in the brain, thereby stabilizing the neurologic features like ambulation, manipulation, swallowing, and language.[1,10] It is advocated for all patients with neurologic, psychiatric, and cognitive manifestations at the time of diagnosis of NPC.[1] The usual recommended dose for adolescent/adult patients is 200 mg oral 3 times a day and should be adjusted according to body surface area in children.[1,10] The clinical improvement is noticeable

Figure MRI brain



MRI brain shows cortical and midbrain atrophy on T1-weighted sequence (A), and cortical atrophy along with subcortical nonspecific white matter changes on fluid-attenuated inversion recovery sequence (B).

Table Neurologic disorders associated with vertical supranuclear gaze palsy (modified from Salsano et al.[8])

Etiology by group	Disorders
Genetic	
Autosomal dominant	Autosomal dominant spinocerebellar ataxia (*SCA1, SCA2, SCA3, SCA6, SCA7, SCA17*)
	Dentatorubral pallidoluysian atrophy
	Autosomal dominant with hereditary spastic ataxia
Autosomal recessive	Kufor-Rakeb disease
	Pantothenate kinase–associated neurodegeneration
	PLA2G6-related dystonia parkinsonism
	Autosomal recessive cerebellar ataxia syndrome with upward gaze palsy, neuropathy, and seizures
	Ataxia telangiectasia
	Nonketotic hyperglycinemia
	Tay-Sachs disease
	Joubert syndrome
Sporadic	Progressive supranuclear palsy
Mitochondrial (autosomal recessive, autosomal dominant, and X-linked)	Leigh syndrome
Structural	Focal midbrain lesion (e.g., from hydrocephalus, stoke, or tumors)
	Following thalamic deep brain stimulation
Metabolic	Kernicterus
	Manganese intoxication
Paraneoplastic	Paraneoplastic brainstem encephalitis (anti-Ma)

by 6 months to 1 year of drug use. The commonly observed side effects are diarrhea, flatulence, abdominal discomfort, weight loss, and tremor.[1,10] While its use in hepatic impairment has not been evaluated, it should be avoided in patients with severe renal impairment (creatinine clearance rate of <30 mL/min/1.73 m^2).[10] Our patient was started on miglustat once genetic diagnosis was made to stabilize his neurologic disease.

We report the second oldest patient at diagnosis with NPC. Myoclonus is not commonly seen in adult-onset NPC, but our patient had myoclonus as one of the major disabling features, along with more commonly reported ataxia and VSGP. Thus, NPC should be suspected in the presence of myoclonus and VSGP. Although increased awareness and improved diagnostic tools have raised the detection rate of NPC, diagnostic delays are still a major concern, especially when substrate reduction therapy using miglustat may stabilize the progression of neurologic disease.

AUTHOR CONTRIBUTIONS

Dr. Kumar: conception, design, and writing the first manuscript. Dr. Rizek: conception, design, review, and critique. Dr. Mohammad: conception, review, and critique. Dr. Jog: review and critique.

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