Late adult-onset Niemann Pick type C (NPC): An “atypical” typical presentation at the age of 62

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Case report

We report a 67-year-old woman with a 5-year history of progressive walking and balance difficulties with near-fall episodes. Gradually she also developed fine motor and speech problems that progressively impacted her communication. Swallowing function was unremarkable, and there was no history of choking episodes in the past. She had an uneventful neonatal period, with normal psychomotor development and unremarkable family history. Past medical history was positive for status post-cholecystectomy, hypertriglyceridemia, gastric bypass surgery (obesity) and mild obstructive sleep apnea. There was no history of hypertension, hypercholesterolemia or diabetes. Patient quitted smoking >5 years ago (23 packs/y).

On examination (video-1), she had a vertical supra-nuclear saccadic palsy (VSSP) without eyelid opening apraxia, nystagmus, skew deviation or pupillary abnormalities. She had no hearing or visual deficits. There was no muscle weakness, and sensory examination was unremarkable. Finger tapping was bilaterally slow but without clear sequence effect. No axial or appendicular rigidity was noticeable. Mild to moderate appendicular and axial ataxia were observed, and postural instability was present in both antero-posterior and medio-lateral directions. During walking, she had a mildly widened base and bilateral reduced arm-swing.

There was an asymptomatic drop in systolic blood pressure (>30 mmHg) immediately after standing-up that quickly recovered after 5 min standing. Urinary incontinence or other dysautonomic features haven’t been found.

The neuropsychological assessment indicated mild perseveration (positive applause-sign) and mild depressive, anxious and apathetic symptoms. Additionally, difficulties in controlling emotions suggestive of pseudobulbar affect were noticed.

Brain MRI is depicted in figure-1. A previous abdominal CT, conducted for an epigastric pain episode, evidenced splenomegaly (14.5 cm [<12 cm]) with a normal-sized liver.

Antibody testing for anti-GAD, anti-endomisium, anti-transglutaminase and paraneoplastic panel (CRMP5, Amphiphysin, Ma2/Ta, Ri, Yo, Hu) were negative. CSF analysis was unrevealing apart from a mild protein elevation (0.70 g/L [0.20–0.40]).

Phenotypically our case fits in the Progressive Supranuclear Palsy (PSP)-like spectrum, with VSSP, gait and balance abnormalities and frontal lobe deficits. Nevertheless, there were important clues suggesting we were facing a different condition. Namely, the presence of cerebellar ataxia, which has only rarely been reported in PSP, the splenomegaly, and the cerebellar atrophy in the absence of clear...
imaging findings suggestive of PSP. Spinocerebellar ataxias (in particular SCA2 and SCA3), can present with ocular motility abnormalities, parkinsonism and dysautonomic features, however VSSP and cognitive abnormalities, as well as the negative family history make this possibility less likely. There were no additional signs suggesting a mitochondrial disorder (like short-stature, impaired hearing/vision, chronic progressive external ophthalmoplegia, diabetes, etc). Anti-Iglon5 disease could present similarly, however the absence of sleep-disorders and the presence of splenomegaly is not common. Lastly, structural lesions involving upper brainstem region, cerebellum, basal ganglia, or respective afferent and efferent pathways can theoretically mimic this phenotype, but the progressive pace of the symptoms and remaining ancillary exams do not support this hypothesis.

Therefore, the hypothesis of alternative diagnosis including neuro-metabolic disorders such as Niemann Pick type C (NPC) and Gaucher’s disease should be considered in such cases, even above 60-years-of-age [1]. The involvement of ocular vertical system instead of the horizontal makes NPC more likely.

The Niemann-Pick suspicious index was 185 (>70 indicating strong suspicious). Plasma oxysterols (Cholestane-3b,5a, 6b-triol and 7-Ketocholesterol) were elevated with values of 53 μg/L and 125 μg/L (<40 and <75, respectively) and reconfirmed in a separate sample. Subsequent genetic analysis for NPC1 confirmed compound heterozygosity for c.180G>T/p.Gln60His, classified as variant of uncertain significance (VUS); and c.3182T>C/p.Ile1061Thr classified as pathogenic variant. Previous in-silico predictions of this VUS with PolyPhen2, SIFT, and Mutation Taster interpreted this variant as likely causative for NPC in two of these tools [2-4].

The majority of adult-onset forms are diagnosed within the 2nd and 3rd decade, yet there is an increasing number of reported cases starting after 50 years [3,5]. To the best of our knowledge, this is the latest manifest case of NPC reported. Previously, the latest case reported had symptom-onset at 54 years [6], and presented a more severe phenotype, with prominent cognitive dysfunction and chorea. In Table 1, we present a detailed description of NPC patients reported in literature with onset after the age of 40. The present patient had a milder phenotype, but shared similar MRI findings including cerebellar atrophy and periventricular signal intensities in T2-weighted images as well as increased CSF protein. In fact, focal changes in grey matter were suggested to be more apparent in adults due to less severe biochemical abnormalities [7]. Similar distribution of the T2 hypersignal lesions have been reported in another patient with onset of the symptoms at the age of 46 (Table 1) [8]. Therefore, we argue that the cribriform lesions seen in the basal ganglia and dentate nucleus of our patient may be disease-related. Leptomeningeal thickening due to neuronal accumulation of sphingolipids and cholesterol may cause this perivascular space enlargement and ultimately neuronal death and gliosis.

Although some genetic mutations have been associated with worse metabolic and clinical phenotypes, a wide genetic variability exists, and even in monozygotic twins distinct phenotypes were described [9]. Features seen in infantile-onset cases such as jaundice, hepatosplenomegaly, “gelastic” cataplexy and seizures are less frequent in later-onset cases, while over 25% can initially manifest with psychiatric symptoms.

As a result, it is thought that NPC may be under-diagnosed, particularly in adult-onset cases where it can resemble more common neurodegenerative disorders [5,10].

Fig. 1. Brain MRI showing multiple small lesions with hypersignal in T2 weighted images (T2W) with small spotty lesions and cribriform changes suggestive of enlarged perivascular (Virchow-Robin) spaces in the dentate nucleus, globus pallidus and caudate nucleus. In the Pons, there were additional white matter lesions with hypersignal in T2 and variable appearance on T1 weighted images (T1W). There were no clear findings compatible with Hummingbird sign (typically seen in PSP), hot cross bun or putaminal rim signs (supportive imaging features of multiple system atrophy). Note the midline and hemispheric cerebellar atrophy in the T1-weighted-sequences.
### Table 1
Detailed literature review of all patients reported with age of onset of neurological symptoms after the age of 40 (for additional details regarding the search strategy used, please see supplementary material).

<table>
<thead>
<tr>
<th>Author</th>
<th>Age at onset</th>
<th>Gender</th>
<th>First neurological symptom</th>
<th>Motor Phenomenology</th>
<th>Cognitive/Psychiatric features</th>
<th>Brain imaging findings</th>
<th>Others</th>
<th>Oxysterol levels</th>
<th>Genetic findings &amp; diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balázs et al., 2019</td>
<td>41y</td>
<td>Male</td>
<td>Hearing loss;</td>
<td>Parkinsonism with postural instability (not levodopa responsive); Ataxia; CIB phenotype; Dysarthria; VSGP; Cerebellar ataxia; Frequent falls; Dysarthria; Dysphagia; Bilateral ptosis; Cranio-cervical dystonia; Stimulus-sensitive myoclonus;</td>
<td>Dementia (decreased verbal fluency, concretization, mild perseveration); Orafacial apraxia; Balint’s syndrome; Cognitive decline with changes of personality (lack of criticism) and affection; Visual and hearing hallucinations with the sense of fear and depression; Mood lability, loquacity, delusions, and hypervigilance; Auditory hallucinations; Paranoid, hyper-religious, and obsessive thoughts; Dementia;</td>
<td>Brain MRI: Mild atrophy</td>
<td>- Hepato-splenomegaly; - 0.196 ng/mL</td>
<td>NPC1 c.2861C &gt; T (S954L) + c.3019C &gt; G (P1007A)</td>
<td></td>
</tr>
<tr>
<td>Tomic et al., 2018</td>
<td>43y</td>
<td>Female</td>
<td>Hearing loss;</td>
<td>Parkinsonism (bradykinesia without decrement); Cerebellar ataxia; Frequent falls; Dysarthria; Ataxia; Parkinsonism; VSGP; Cranio-cervical dystonia; Stimulus-sensitive myoclonus;</td>
<td>Cognitive impairment; Pseudobulbar affect; Mood lability, loquacity, delusions, and hypervigilance; Auditory hallucinations; Paranoid, hyper-religious, and obsessive thoughts; Dementia;</td>
<td>Brain MRI: Mild cortical atrophy; Periventricular demyelinating lesion (+ frontal lobes) DaTSCAN: unilateral deficit grade I on the right side;</td>
<td>- Incontinence; - Sensorimotor neuropathy - Glomerulonephritis (unknown etiology)</td>
<td>Not reported; No genetic test performed. Positive Filipin staining test in skin fibroblasts.</td>
<td></td>
</tr>
<tr>
<td>Josephs et al., 2003</td>
<td>46y</td>
<td>Female</td>
<td>Depression and hypersomnolence;</td>
<td>-</td>
<td>Mood lability, loquacity, delusions, and hypervigilance; Auditory hallucinations; Paranoid, hyper-religious, and obsessive thoughts; Dementia;</td>
<td>Brain MRI: Small foci of increased T2 signal changes within pons and cerebral white matter;</td>
<td>Not reported; No genetic test performed. Positive Filipin staining test in skin fibroblasts.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbeek et al., 2017</td>
<td>48y</td>
<td>Female</td>
<td>Balance problems;</td>
<td>Cerebellar ataxia; Parkinsonism (bradykinesia without decrement); Postural instability; Hyperreflexia; Dysarthria; Dysphagia; VSGP;</td>
<td>Cognitive impairment; Pseudobulbar affect;</td>
<td>Brain MRI: Mild to moderate cerebral and cerebellar atrophy; DaTSCAN: marked symmetrical loss of dopamine transporter binding (+ putamen);</td>
<td>- Sensorineural hearing loss (since childhood) - Mild splenomegaly;</td>
<td>Not reported; No genetic test performed. Positive Filipin staining test in skin fibroblasts.</td>
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<tr>
<td>Kumar et al., 2016</td>
<td>50y</td>
<td>Male</td>
<td>Hearing loss;</td>
<td>Ataxia; Myoclonus (trunk and upper extremities); VSGP;</td>
<td>Normal cognition;</td>
<td>Brain MRI: Cortical and midbrain atrophy with subcortical nonspecific white matter changes;</td>
<td>Not reported;</td>
<td>Not reported; NPC1 c.3019C &gt; G (P1007A) + c.3230G &gt; A (R1077Q)</td>
<td></td>
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<tr>
<td>McFarlane et al., 1988</td>
<td>51y</td>
<td>Male</td>
<td>Clumsiness and unsteadiness;</td>
<td>Cerebellar ataxia; Dysarthria; VSGP; Rigidity;</td>
<td>Not reported</td>
<td>Brain CT: Cerebral atrophy;</td>
<td>Pallor of right optic disc; Sensitive neuropathy; Positive globellar tap;</td>
<td>Not reported; No genetic test performed. Autopsy confirmed case. NPC1 K1206fs + no other mutation identified at that time in the other allele. Positive Filipin staining test in skin fibroblasts.</td>
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<tr>
<td>Trendelenburg et al., 2006</td>
<td>54y</td>
<td>Female</td>
<td>Cognitive impairment; and depression</td>
<td>Depression and fluctuating mood; Dementia with reduced impulse and affective instability;</td>
<td></td>
<td>Brain MRI: Mild cerebellar atrophy; Periventricular signal intensities in the T2/TIRM; Brain FDG-PET: Bilateral hypometabolism in thalamic and parietooccipital cortical regions;</td>
<td>Increased CSF protein (73.7 mg/dl); MILD splenomegaly (14 cm);</td>
<td>Not reported;</td>
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</table>

Abbreviations: VSGP - Vertical Supranuclear Gaze Palsy; y – years.
References


