Later life cognitive impairment: an ophthalmological diagnostic clue?

Phyu Phyu Aung MRCPsych, Shahd Hamid MRCP, Andrew J Larner MD, PhD

Although cognitive impairment in later life is often due to neurodegenerative and cerebrovascular disease, precise diagnosis may sometimes be difficult, particularly in the context of multi-morbidities. In addition, although the genetic aetiology of neurological diseases is increasingly defined, the full spectrum of clinical features associated with particular genetic mutations may be uncertain. Here the authors present a case that illustrates some of these problems, and in which neurological signs may have been a clue to the underlying cognitive diagnosis.

Diagnosing the cause of cognitive impairment in later life can be challenging. While textbook accounts of common disease archetypes, for example Alzheimer’s disease and vascular dementia, may seem clear cut and give the impression that diagnosis is straightforward, day-to-day clinical practice is often less exact, particularly in the context of the multi-morbidities which often accrue with ageing. In addition, the full phenotypic spectrum of disorders only relatively recently defined at the neurogenetic level may not yet be fully apparent, complicating diagnostic reasoning. We present a case illustrating such difficulties.

Presentation
A 68-year-old right-handed lady attended the cognitive disorders clinic with her sister. She reported an approximately six-month history of memory problems, such as forgetting appointments and difficulty following conversations, and requiring a blister pack to recall when to take her medications, but she was managing all instrumental activities of daily living (iADLs). Neurological examination showed partial ptosis, bilaterally symmetrical, and external ophthalmoplegia. There was no evidence of muscular weakness or fatigability, and no parkinsonian signs.

The ptosis and external ophthalmoplegia had first been noted in her fortieths, and was also present in several other family members (including the patient’s mother and maternal grandfather) in a pattern suggesting autosomal dominant transmission. A mitochondrial disorder, autosomal dominant progressive external ophthalmoplegia (adPEO), was suspected on the basis of this phenotype and family history. Muscle biopsy showed ragged red fibres with approximately 20% of fibres negative for cytochrome c oxidase (COX). Skeletal muscle DNA showed multiple mitochondrial DNA rearrangements. Subsequent genetic testing showed a novel heterozygous mutation (c.1374G>T, p. Q458H) in exon 2 of the PEO1 gene encoding the Twinkle helicase protein, a finding included in a publication by Fratter et al. documenting a series of patients with adPEO (probably case 22, although the family details given in the publication differ from those we elicited from the patient).1

There was also a previous history of non-traumatic non-aneurysmal intraventricular haemorrhage in the patient’s early fifties, complicated by secondary hydrocephalus requiring shunting, from which she made a good recovery following a period of rehabilitation.

Investigation of her cognitive symptoms included administration of screening instruments on which she performed well, scoring 28/30 on the Mini-Addenbrooke’s Cognitive Examination (MACE)2 and 28/30 on Free-Cog (subscores: cognitive function 23/25; executive function 5/5).3 However, on an informant scale, Ascertain Dementia 8 (AD8),3 completed by her sister, the patient scored poorly (8/8, where higher score = worse outcome). Hence she was referred for formal neuropsychological assessment, which showed only mild memory impairment (eg Wechsler Memory Scale IV, Delayed Memory 19th percentile), preserved visuospatial and language-based tasks, but difficulties with executive functioning (eg Trail Making Test 1st percentile) and processing speed (eg Wechsler Adult Intelligence Scale-IV, processing speed 5th percentile). On the Hospital Anxiety and Depression scale she scored in the moderate range for anxiety and the mild range for depression.

Structural brain (magnetic resonance [MR]) imaging showed global brain atrophy and some minor small vessel ischaemic changes; shunt placement and function appeared satisfactory. Functional brain imaging with 99mTcTechnetium hexamethylpropylene amine oxime single-photon emission computed tomography (99mTc HMPAO-SPECT) showed globally reduced perfusion with a greater emphasis anteriorly than posteriorly with relative preservation of high parietal, occipital and inferior frontal regions. Repeat administration of
cognitive screening instruments two years after initial assessment in the cognitive clinic showed stable scores (MACE 27/30; Free-Cog 28/30, subscores 23/25 and 5/5).

Discussion
This patient’s phenotype was not that of Alzheimer’s disease; she was not amnesic, had no visuospatial impairments, had preserved iADLs, no focal medial temporal lobe or hippocampal atrophy on structural (MR) brain imaging, and no temporoparietal hypoperfusion on SPECT imaging. In addition, neither vascular cognitive impairment nor frontotemporal lobar degeneration were thought likely, based on cognitive phenotype, absence of suggestive neurological signs or vascular risk factors, and neuroimaging findings. While the previous brain haemorrhage might be a factor, this was thought unlikely in view of its remote occurrence, more than 15 years before the onset of the current symptoms. We were therefore left to question whether the cognitive symptoms were a consequence of her mitochondrial disorder. While acknowledging that this could be simply a chance concurrence, a number of factors potentially implicate this genetic disorder.

Mitochondrial adPEO is often a ‘pure’ condition but may sometimes be attended by additional neurological features (‘ophthalmoplegia-plus’), including cognitive impairment. Zierz et al. noted dementia in four of 31 adPEO patients (13%). Various genetic causes for adPEO have now been defined, including mutations in genes encoding Twinkle helicase protein, ANT1, and OPA1. Cognitive impairment and dementia have been noted on occasion in previous reports of Twinkle mutations. Two families with the R374W mutation developed late-onset dementia as part of a multisystem disorder characterised by hearing loss, myopathy, dysphagia, dysphonia, sensory neuropathy, as well as PEO,7 hence entirely unlike our patient. In a literature review, Martin-Negrier identified dementia in 4 of 35 Twinkle mutation cases (11%).8 But these did not include our patient’s mutation (p.Q458H). Systematic accounts of neuroimaging, either structural or functional, in Twinkle mutation patients have, unsurprisingly, not been found. Cognitive impairment has been documented on occasion with other genetic causes of adPEO, such as ANT19 and OPA1. Mitochondrial disorders may show a variable phenotype, despite the same underlying genetic mutation. The relative paucity of accounts of cognitive impairment in previous reports of Twinkle mutations does not, therefore, preclude the possibility that they may be associated with cognitive impairment and dementia, with onset perhaps many years after the onset of ophthalmological features. More generally, cognitive decline or dementia, sometimes characterised as ‘mitochondrial dementia’ is reported in various mitochondrial syndromes. The pattern is variable, but generally there are specific cognitive deficits, particularly in visual construction, attention, abstraction, or flexibility but without a general intellectual deterioration.11 The differential diagnosis of mitochondrial dementia and symtomatic dementia may be difficult, particularly in later life.9

More prolonged follow-up may clarify our patient’s diagnosis. We suggest that there may be a case for monitoring of patients who harbour mitochondrial mutations for cognitive decline, for example with brain imaging, including MR spectroscopy, to look for lactate peaks. Although no specific treatment is currently available for mitochondrial disease, this is an area of much research in the hope of discovering disease-modifying treatments. These might impact on cognitive impairment not only in mitochondrial disease but also possibly in other disorders where mitochondrial dysfunction occurs, such as Alzheimer’s disease.12

Declaration of interests
No conflict of interests were declared.

Dr Aung is a Specialist Registrar in Old Age Psychiatry, Dr Hamid is a Specialist Registrar in Neurology and Dr Larner is a Consultant Neurologist, all at the Walton Centre for Neurology and Neurosurgery, Liverpool.

References