Clinical Pathologic Conference

A Young Man With Progressive Vision and Hearing Loss

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A 37-year-old man with a history of progressive bilateral sensorineural hearing loss presented to the neuro-ophthalmology clinic with an acute left homonymous hemianopsia. In this article, we discuss the clinical approach and differential diagnosis of progressive combined vision and hearing loss and guide the reader to discover the patient’s ultimate diagnosis.

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Report of a Case

A 37-year-old man with a history of progressive hearing loss presented to the neuro-ophthalmology clinic in 2014 with 1 month of decreased vision in his left visual field. He also reported a period of binocular horizontal diplopia, similar in all directions of gaze, that had since resolved. Medical history revealed bilateral synchronously progressive hearing loss since 2003, resulting in complete hearing loss by 2009. Intratympanic steroids provided no benefit, and he was subsequently treated with bilateral cochlear implantation. He took no medications and had no allergies. He had a normal neurodevelopmental history. There was no family history of stroke or hypercoagulable disease, but several maternal aunts had early hearing loss requiring the use of hearing aids. He was single and employed as an engineer. He denied any alcohol, tobacco, or drug use; any dizziness or unsteadiness; and any fluctuation in his hearing during his period of progressive hearing loss. He also did not reside in a tick-endemic region of the country.

On neurologic examination, visual acuity was 20/25 in both eyes with correction. He correctly identified 11 of 11 Ishihara color plates in both eyes. Pupils were 5 mm and bilaterally reactive with no relative afferent pupillary defect. Motility was full, and alignment showed a 10–prism diopter esophoria in all cardinal directions of gaze. Confrontation and Humphrey visual fields showed a left homonymous hemianopsia. Anterior slitlamp examination was normal. Dilated fundus examination revealed normal optic discs with a cup-disc ratio of 0.2 bilaterally. Both maculae were flat, and the peripheral retinas were normal. His strength and sensation were normal in all 4 extremities.

Laboratory and Radiologic Data

A computed tomographic scan of the head performed at presentation showed a right medial occipital hypodensity and bilateral basal ganglia calcifications (Figure). Laboratory testing identified no traditional factors for ischemic stroke. Complete blood cell count and electrolyte results were normal. Hemoglobin A1c was 5.3% (to convert to proportion of total hemoglobin, multiply by 0.01). Low-density lipoprotein cholesterol level was 128 mg/dL (to convert to micromoles per liter, multiply by 0.0259). Erythrocyte sedimentation rate was 6 mm/h (to convert to millimeters per hour, multiply by 1), and C-reactive protein level was 0.4 mg/L (to convert to nanomoles per liter, multiply by 9.524). Test results for rapid plasma reagin and fluorescent treponemal antibody were negative. Results for antinuclear antibodies and rheumatoid factor were negative. Results for hypercoagulability testing with activated protein C resistance, anticardiolipin antibodies, and β2 glycoprotein antibodies showed no abnormalities. Leukocyte α-galactosidase activity was normal.

Transesophageal echocardiogram results showed normal cardiac function without masses or thrombi. Computed tomographic angiography of the head and neck revealed no areas of stenosis. A second head computed tomography was subsequently performed 2 months after his initial presentation when he reported apraxia and left arm weakness, which showed resolution of the medial occipital lesion with a new hypodensity in the right posterior frontal lobe (eFigures 1–9 in the Supplement).

Clinical Discussion (Dr Kung)

This patient presented with a new left homonymous hemianopsia in the setting of profound progressive sensorineural hearing loss and a maternal family history of early hearing loss.

Although this patient’s vision loss localized well to the right occipital lobe, vision loss can localize to the anterior chamber, retina, retinal vasculature, optic nerve, or cerebral cortex. When combined with the presence of sensorineural hearing loss, the diseases that are known to cause combined vision and hearing loss can be subdivided by category of disease and by the localization of the visual disturbance (Table).

Infectious causes of combined vision and hearing loss include syphilis and Lyme disease. While miotic pupils with light-near dissociation (ie, Argyll Robertson pupils) are classically seen in neurosyphilis, there are many potential ocular manifestations including uveitis, chorioretinitis, neuroretinitis, retinal vasculitis, and acute, subacute, or chronic optic neuropathy. Furthermore, syphilis should...
alsobespecificallyconsideredincasesofacuteorsubacutesensorineuralhearinglossbecausethisoneofonlyseveralpotentiallyreversiblecausesofsensorineuralhearingloss.\(^1\)

Inendemicareas,Lymediseaseshouldbeconsideredbecausemayproduceproteanocularmanifestationswithsensorineuralhearinglosssimilartosyphilis.Inthispatient,testresultsforspeedplasmareaginandfluorescenttreponemalantigenantibodieswerenegative,andeheidnotresideinaLyme-endemicarea,makingtheseinfectiousetiologiesunlikely.

Onceinfectiouscauseshavebeenexcludedincasesofcombinedvisionandhearingloss,autoimmuneandinflammatorydisordersshouldbeconsideredgiventhepotentialforcorticosteroidsandimmunosuppressantsissignificantlyimproveoralterthecourseofthesediseases.

Cogan syndromeisanautoimmunedisordercharacterizedbytheacute-to-subacutepresentationofvisualdisturbancesowingtointerstitialkeratitiscombinedwithMeniere-likeattacksofhearingloss,tinnitus,andalong.\(^{2}\)Nearlyallpatientseventuallydevelopsensorineuralhearingloss,andifleftuntreated,hearinglosscanbecomeprofound.Theocularmanifestationsofinterstitialkeratitisincludeeyeredness,eyepain,sensitivitiltytolight,andblurredvision.

Youngadultsareclassicallyaffected,althoughcasesinchildrenand
A Young Man With Progressive Vision and Hearing Loss

older adults have also been reported. Rarely, a systemic vasculitis may also be present.

Susac syndrome is another inflammatory microvasculopathy characterized by the clinical triad of encephalopathy, branch retinal artery occlusions, and vascular hearing loss.3 Brain magnetic resonance imaging classically shows infarctions within the body of the corpus callosum. Because of the ongoing autoimmune microvasculopathy, serial retinal infarctions may lead to cumulative and irreversible vision loss. Vascular hearing loss may also occur abruptly and be associated with poor speech discrimination, vertigo, and tinnitus.

Vogt-Koyanagi-Harada is a rare disorder in which tissues containing melanocytes are targeted, leading to a constellation of bilateral uveitis with sensorineural hearing loss, tinnitus, and vertigo, which may be associated with vitiligo, alopecia, or poliosis (loss of melanin in head hair, eyebrows, or eyelashes).4 When treated early, the prognosis for vision is reported to be favorable.

Giant cell arteritis is also occasionally associated with acute symptomatic hearing loss that can precede the visual symptoms.5 Therefore, if a patient develops acute or subacute hearing loss in association with headaches, jaw claudication, or other systemic symptoms, giant cell arteritis should still be strongly considered. Acute posterior multifocal placoid pigment epitheliopathy should be considered in cases of acute to subacute visual loss with evidence of multiple discrete yellow-white placoid lesions in the retina because this entity is rarely associated with a catastrophic cerebral vasculitis.6

Other potentially reversible inflammatory and infiltrative causes of combined vision and hearing include amyloidosis, sarcoidosis, superficial siderosis, pachymeningitis (including IgG 4–related disease), neurolymphomatosis, and other forms of systemic vasculitis.7 However, in these diseases, other symptoms are likely to be more prominent than the presence of isolated visual or audiovestibular dysfunction.

This patient’s hearing loss was gradually progressive over a period of approximately 6 years, making a unifying autoimmune or inflammatory etiology exceedingly unlikely. Furthermore, his vision loss was owing to cerebral cortical involvement rather than involvement of the eye itself, and his hearing loss was gradually progressive without dizziness, unsteadiness, or attacks of vertigo. Therefore, metabolic and hereditary etiologies should be considered.

In the category of metabolic diseases, Refsum disease, a peroxisomal disorder, may present with a combination of early night blindness owing to retinitis pigmentosa, gradually progressive sensorineural hearing loss, and evidence of cerebellar ataxia with a superimposed sensory ataxia from demyelinating polyneuropathy.8 Fabry disease, a lysosomal storage disorder, may present in young adults with cortical vision loss owing to ischemic stroke, mild sensorineural hearing loss, painful peripheral neuropathy, renal failure, and congestive heart failure.9 Several other inherited diseases known to cause combined vision and hearing loss include Usher syndrome, which presents with retinitis pigmentosa and early profound sensorineural hearing loss10; Wolfram syndrome, which presents in early childhood with optic atrophy, high-frequency hearing loss, and diabetes insipidus or mellitus11; and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss syndrome. In this male patient, while there are findings suggestive of a cerebral infarct, such as in Fabry disease, his normal α-galactosidase activity precludes this diagnosis.

Finally, there are also a number of named mitochondrial disorders to consider in patients with combined vision and hearing loss. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a mitochondrial disorder that classically presents in young adults with recurrent or sequential stroke-like symptoms.11 However, the affected cortical areas tend not to conform to a typical vascular distribution, and the symptoms and imaging may improve more than expected for ischemic stroke. The posterior cerebral lobes are classically involved, often leading to homonymous cortical visual field defects. Bilateral basal ganglia calcifications may be present, a finding that can be seen in mitochondrial disease and a number of other inherited, infectious, toxic, or metabolic conditions such as cytomegalovirus or rubella infection, AIDS, carbon monoxide poisoning, Fahr syndrome (familial idiopathic basal ganglia calcification), and hyperparathyroidism or hypoparathyroidism. Lactate levels are classically elevated in MELAS, although other manifestations are variable, including hearing impairment, migraines, muscle weakness, cardiomyopathy, peripheral neuropathy, learning disabilities, dementia, and/or epilepsy. The disease is maternally inherited, and a careful family history often reveals affected maternal female relatives. Neuropathy, ataxia, and retinitis pigmentosa is another mitochondrially inherited disease with its named features as cardinal symptoms, particularly with regard to its severe sensorimotor polyneuropathy and progressive visual impairment from retinitis pigmentosa. Hearing loss is variable.11 Dominant optic neuropathy may also be occasionally associated with hearing loss, known as dominant optic neuropathy–plus.12

Table. Differential Diagnosis

<table>
<thead>
<tr>
<th>Category of Disease</th>
<th>Possible Diagnosis</th>
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<tbody>
<tr>
<td>Infectious</td>
<td>Syphilis and Lyme</td>
</tr>
<tr>
<td>Autoimmune/inflammatory</td>
<td>Cogan syndrome, Susac syndrome, Vogt-Koyanagi-Harada syndrome, giant cell arteritis, and acute posterior multifocal placoid pigment epitheliopathy</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Refsum disease and Fabry disease</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Usher syndrome; Wolfram syndrome; and cerebral ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss syndrome</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; neuropathy, ataxia, and retinitis pigmentosa syndrome; dominant optic atrophy–plus</td>
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This patient’s history of 2 stroke-like episodes, sensorineural hearing loss, and family history of several maternal relatives with early hearing loss strongly suggest MELAS. Further diagnostic testing, including lactate/pyruvate levels, muscle biopsy, and/or genetic testing, should be performed.

Clinical Course
Following the patient’s initial presentation, plasma lactate was found to be elevated at 23.42 mg/dL (normal levels, 5.0-15 mg/dL [to convert to millimoles per liter, multiply by 0.111]), and pyruvate was elevated at 0.10 mmol/L (normal levels, 0.03-0.08 mmol/L) with a normal lactate-pyruvate ratio of 26 (normal levels, 10-30). Blood was then sent for leukocyte testing to evaluate for several of the most common mutations in MELAS, results of which returned negative. However, owing to the high suspicion for mitochondrial disease, a left gastrocnemius muscle biopsy was performed.

Pathology
Histologic analysis of the patient’s muscle fibers showed no ragged red fibers on the Gomori trichrome stain. Cytochrome c oxidase was qualitatively decreased, although there was a relative abundance of type 2b muscle fibers. In addition, there were no fibers or blood vessels with increased staining on succinate dehydrogenase (eFigures 1-9 in the Supplement). The muscle was subsequently sent for comprehensive mitochondrial genomic analysis by next-generation sequencing, which revealed a pathogenic 97.7% heteroplasmic 1644 glycine to alanine point mutation in the mitochondrially encoded transfer ribonucleic acid for valine, confirming the diagnosis of MELAS.

Conclusions
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes is classically a maternally inherited mitochondrial disorder characterized by stroke-like episodes before age 40 years, encephalopathy owing to seizures or dementia, and myopathy characterized by lactic acidosis and/or ragged red fibers. Most cases are caused by a pathogenic 3243 alanine to glycine mutation in mitochondrially encoded tRNA-leucine, although at least 14 other mitochondrial point mutations and at least 1 nuclear gene mutation can also produce a MELAS phenotype.

The pathophysiology of MELAS is incompletely understood but relates broadly to insufficient energy production through the oxidative phosphorylation pathway. The cerebral vasculature also appears to be selectively susceptible to energy failure in MELAS, leading to the stroke-like episodes seen in this syndrome. l-arginine, a nitric oxide precursor, has been explored as a treatment for these episodes.

When mitochondrial diseases are suspected, the evaluation typically begins with biochemical testing including lactate and pyruvate levels, muscle biopsy for histologic examination, mitochondrial enzymatic analysis, and mitochondrial genomic analysis. However, normal histologic and mitochondrial enzymatic findings in muscle do not preclude a diagnosis of mitochondrial disease, as demonstrated in this case.

Each human cell contains thousands of individual copies of mitochondrial DNA, and normal wild-type mitochondrial DNA often coexist with pathogenically mutated mitochondrial DNA, a state known as heteroplasmy. When each cell subsequently divides, there is then random segregation of mitochondria and mitochondrial DNA into the daughter cells, which ultimately leads to a nonuniform distribution of affected mitochondria into various tissues (eg, into leukocytes, liver, or muscle). Therefore, genomic testing should be performed on affected tissue, especially those which are enriched in mitochondria (eg, appendicular muscle).

Once the exact genetic mutation is identified, this information will help to identify and anticipate the known complications of the patient’s syndrome and will likely continue to guide the patient’s care well into the future.

REFERENCES