Elevated lipoprotein(a) levels as the cause of cryptogenic stroke in a young Ashkenazi Jewish female

Lipoprotein(a) is a cholesterol carrier molecule, structurally similar to low-density lipoprotein (LDL), but with distinct properties predisposing it to associations with increased risk of stroke, myocardial infarction (MI), and aortic stenosis.[1–4] However, lipoprotein(a) levels are not routinely checked, although there is a known pattern of genetic inheritance.[5] We present a case of a young patient with purported cryptogenic stroke and a family history of cardiovascular disease, which was attributed to elevated lipoprotein(a) levels. To our knowledge, this is the first reported case of lipoprotein(a)-related thalamic infarct presenting with neuro-ophthalmic findings in the English-language ophthalmic literature.

A 38-year-old female presented with acute painless diplopia and ataxia with "inability to stand." Her medical history included only gastroesophageal reflux disease and latent tuberculosis treated 1-year ago. She had a remote (16 years ago) history of occasional cigarette smoking. Family history revealed cardiovascular problems in the father, including MI at age 60 years treated with coronary artery bypass grafting, aortic stenosis treated with balloon valvuloplasty, and thoracic aortic aneurysm with dissection and repair at age 61 years. The patient's parents were Ashkenazi Jewish.

On ophthalmologic examination, visual acuity was 20/20 OU. Pupils were reactive and symmetric, with no relative afferent pupillary defect (RAPD). Slit-lamp biomicroscopy, intraocular pressure, confrontation visual fields, and fundus examinations were normal OU. External examination revealed a 1 mm ptosis OD and minimal lid retraction OS. There was no arcus senilis or xanthelasma noted. Lifting the ptotic lid OD did not change the lid position OS, consistent with a true "plus-minus" syndrome. Extraocular motility showed a moderate underaction of elevation and adduction OS and underaction of elevation OD, consistent with a partial third nerve palsy OD and a superimposed bilateral upgaze and/or contralateral superior rectus palsy OS. This combination of findings localizes to the right thalamo-mesencephalic junction involving the right fascicular third nerve (ptosis OD), dorsal midbrain lid retraction (Collier sign OS), posterior commissure (upgaze palsy OU), and contralateral superior rectus subnucleus (Fig. 1).

Findings of initial computed tomography (CT) scan head and CT angiography (CTA) head and neck were normal. Tissue plasminogen activator (tPA) was administered, and the patient was admitted to the hospital. Overnight, her symptoms worsened with new dysarthria and left hemiplegia of upper and lower extremities. A repeat CT head was negative. Magnetic resonance imaging (MRI) brain the next morning showed an acute infarct on diffusion-weighted imaging (DWI) at the level of the right rostral thalamo-mesencephalic junction (Fig. 2).

A complete stroke evaluation, including cardiac monitoring, electrocardiography, transesophageal echocardiography with an agitated bubble study, and transcranial Doppler ultrasonography, showed no patent foramen ovale or cardiac source for emboli. Complete hypercoaguable state evaluation and traditional lipid and cholesterol studies were negative except for an elevated lipoprotein(a) level of 74 mg/dL (normal ≤29 mg/dL). The patient was prescribed atorvastatin 40 mg and aspirin 81 mg. At her 5-month follow-up, the ataxia, diplopia, lid retraction OS, and ptosis OD had resolved, and she only had mild residual upgaze paresis OU.

Lipoprotein(a) is a cholesterol carrier structurally similar to LDL. Like LDL, it is composed of a core of neutral lipids and Apo-B100, but also includes Apo(a) connected by a disulfide bond.[6] Apo(a) is responsible for the notable properties of lipoprotein(a), as it has structural homology to plasminogen, giving it thrombotic properties that may interfere with the conversion of plasminogen to plasmin.[5] Traditional testing of cholesterol uses enzymatic studies to quantify total cholesterol, triglycerides, and high-density lipoprotein (HDL), and LDL-cholesterol is subsequently quantified by mass, indirectly, using the Friedewald equation. In contrast, lipoprotein(a) testing is quantified by mass with a direct antibody assay, although standardization is limited by the heterogeneity of particle size.[7]

Lipoprotein(a) is associated with an increased risk of stroke. A meta-analysis of 20 studies showed a pooled odds ratio (OR) of 1.41 and a relative risk (RR) of 1.29 ($p < 0.01$).[1] The risk is higher for younger patients (mean age <55 years), with an OR of 1.94 and RR of 1.36.[1] In the Copenhagen City Heart Study, elevated lipoprotein(a) levels led to a stepwise increased risk of MI, with adjusted hazard ratios of up to 3.6–3.7.[2] Other studies have linked elevated lipoprotein(a) to development of aortic stenosis via rapid calcification, with a larger effect size than seen for elevated LDL levels.[3,8] This patient's father had aortic stenosis and other cardiovascular disease and her mother also had elevated lipoprotein(a) levels. In a study of familial hypercholesterolemia in Israel, variant alleles of the *Apo(a)* gene were identified in 4 ethnic groups, among them were Ashkenazi Jewish patients with an associated 30%–33% increase in lipoprotein(a) levels.[9] Significant differences in lipoprotein(a) structure, levels, and subsequent stroke and cardiovascular risk have been noted between different ethnic populations.[10] In a case-control study of young to middle-aged adults, lipoprotein(a) levels were found to be positively associated with cryptogenic strokes in white patients, but not in black or Hispanic subgroups.[11] Therefore, additional research is needed to further characterize those patients at higher risk, in whom screening for lipoprotein(a) levels may be indicated, before development of cardiovascular events.

Due to the relatively recent recognition of the significance of lipoprotein(a), the association between elevated lipoprotein(a) levels and ophthalmic findings of systemic lipid abnormalities such as xanthelasma or arcus senilis is unclear. Two small-scale studies conducted on patients with xanthelasma did not find significant elevations in lipoprotein(a) levels compared to controls.[12,13]

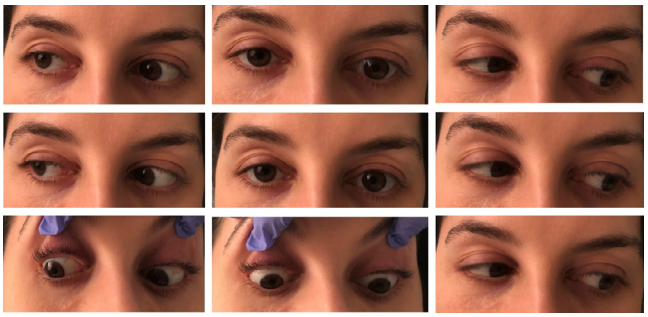

Fig. 1—External and extraocular motility examination demonstrates the 1 mm ptosis OD and lid retraction OS; the bilateral underaction of elevation OU (slightly worse OS) in the upper panels; underaction of adduction OS.

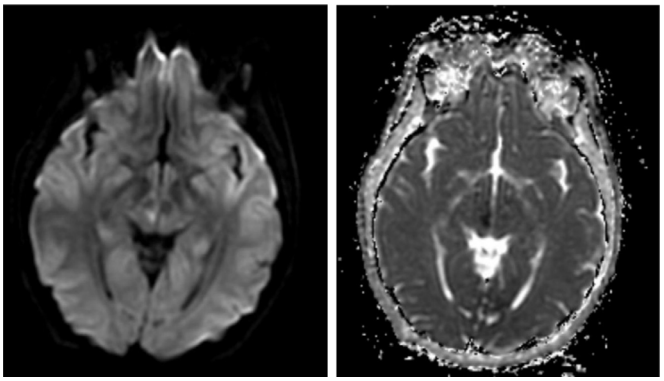

Fig. 2—Magnetic resonance imaging brain with diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC) comparison. Acute infarct noted at right rostral thalamo-mesencephalic junction, likely involving posterior commissure, the right fascicular third nerve, and left superior rectus subnucleus. Appearance is hyperintense on DWI and hypointense on ADC, consistent with appearance of acute stroke. This could produce the right lid ptosis, the left lid retraction, the partial third (OD) nerve palsy, the upgaze palsy, and the superior rectus underaction (OS).

There is no consensus on the treatment for lowering lipoprotein(a) levels, but statins have been reported to lower levels by up to 19%–22%, aspirin by 20%, and niacin by 25%.[10] Newer agents, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have been approved for use and are reported to decrease lipoprotein(a) by 20%–31%.[7,14]

In summary, we describe a case of thalamo-mesencephalic stroke presenting with diplopia, "plus-minus" lid sign, and ataxia due to elevated levels of presumed lipoprotein(a). Although the unique findings of each case are often not documented in the literature, to our knowledge, this is the first and only such case in the English-language ophthalmic literature. We recommend that patients with a negative initial cardiac, vascular, and hematologic evaluation for the more common causes of stroke (especially young patients with presumed cryptogenic stroke) should be considered for lipoprotein(a) testing in addition to traditional hypercoaguabilty and lipid panels.

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References

1. Nave AH, Lange KS, Leonards CO, et al. Lipoprotein(a) as a risk factor for ischemic stroke: a meta-analysis. *Atherosclerosis*. 2015;242:496–503.
2. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation*. 2008;117:176–84.
3. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368:503–12.
4. Malaguarnera M, Vacante M, Russo C, et al. Lipoprotein(a) in cardiovascular diseases. *Biomed Res Int*. 2013;2013:650989.
5. Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res*. 2016;57:1339–59.
6. Utermann G. The mysteries of lipoprotein(a). *Science*. 1989;246:904–10.
7. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol*. 2017;69:692–711.
8. Yu B, Khan K, Hamid Q, et al. Pathological significance of lipoprotein(a) in aortic valve stenosis. *Atherosclerosis*. 2018;272:168–74.

9. Leitersdorf E, Friedlander Y, Bard JM, Fruchart JC, Eisenberg S, Stein Y. Diverse effect of ethnicity on plasma lipoprotein[a] levels in heterozygote patients with familial hypercholesterolemia. *J Lipid Res*. 1991;32:1513–9.
10. Koschinsky ML, Boffa MB. Lipoprotein(a): an important cardiovascular risk factor and a clinical conundrum. *Endocrinol Metab Clin North Am*. 2014;43:949–62.
11. Beheshtian A, Shitole SG, Segal AZ, et al. Lipoprotein (a) level, apolipoprotein (a) size, and risk of unexplained ischemic stroke in young and middle-aged adults. *Atherosclerosis*. 2016;253:47–53.
12. Esmat S, Abdel-Halim MR, Fawzy MM, et al. Are normolipidaemic patients with xanthelasma prone to atherosclerosis? *Clin Exp Dermatol*. 2015;40:373–8.
13. Ozdol S, Sahin S, Tokgozoglu L. Xanthelasma palpebrarum and its relation to atherosclerotic risk factors and lipoprotein (a). *Int J Dermatol*. 2008;47:785–9.
14. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med*. 2012;367:1891–900.

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Optic neuropathy in extramedullary, blast crisis of chronic myeloid leukemia

Chronic myeloid leukemia (CML) represents 10%−20% of all leukemias. Vision loss in patients with CML is usually related directly to the disease (CML) or less likely to potential side effects of the treatment of CML (e.g., radiotherapy or chemotherapy). Extramedullary CNS or meningeal blast crisis in CML is an uncommon but well-known complication of CML. Visual loss in CML typically occurs with abnormal serum white blood cell (WBC) count, peripheral blood smear, bone marrow biopsy, cerebrospinal fluid (CSF) analysis, or neuroimaging. We describe a unique case of vision loss and optic nerve atrophy as the presenting and only sign of extramedullary CNS, CML blast crisis in a patient with initial negative serum, CSF, and neuroimaging. To our knowledge this is the first such case to be described in the English-language ophthalmic literature Table 1.

A 63-year-old man presented with chronic, progressive, painless, and bilateral asymmetric (left worse than right) central vision loss. Two years before presentation he was diagnosed with Philadelphia chromosome positive and CML and treated with hydroxyurea, imatinib, inotuzumab ozogamicin, bosutinib, and blinatumomab. At initial diagnosis, intrathecal treatment with liposomal cytarabine was administered after a lumbar puncture was positive for CNS involvement. His CSF turned negative after the fifth dose of cytarabine with good response (polymerase chain reaction [PCR] of 1.75%) and he reached minimal residual disease (MRD). Serial serum and CSF PCRs confirmed that he was stable. However, the patient relapsed showing 79% blasts in the serum for which he was switched to blinatumumab plus ponatinib. Under this regimen of treatment, he achieved complete cytogenetic response (CCyR), and PCR was 0.08%. He then developed adverse effects to ponatinib, including worsening high blood pressure that prompted serial visits to the emergency department (systolic ~200 mm Hg), peripheral neuropathy, and subjective blurry vision; he self-discontinued the medication, without the previous consent or knowledge of his physicians. A complete blood count (CBC) was within normal limits with no blasts. Magnetic resonance imaging (MRI) of the head and orbit was negative, and repeat CSF analysis showed no pleocytosis or blasts. A diagnosis of possible "ponatinib-related ocular toxicity" was made, and the patient was referred to the neuro-ophthalmology service.

His visual acuity was 20/25 OD and counting fingers OS with a left relative afferent pupillary defect. Slit-lamp biomicroscopy; external, extraocular motility; and intraocular pressure examination findings were normal. Fundus examination revealed bilateral optic nerve pallor. No cotton wool patches, arteriolar narrowing, intraretinal hemorrhages, or optic disc

Table 1—Presenting ophthalmological findings in reported cases

	Ophthalmic Findings	MRI and Laboratory Findings
Jain and Gupta[1]	• Bilateral visual loss and retinal hemorrhages	• MRI: Pachymeningeal enhancement and bilateral optic nerve thickening • LP: Myeloid blast cells
Mbekeani et al.[2]	• Profound bilateral vision loss • OD: Counting fingers • OS: Light perception	• MRI: Chiasm and bilateral optic nerve enhancement • LP: Myeloid blast cells • BM: Normal
Schocket et al.[3]	• Painless, progressive left eye vision loss • OD: 20/20 • OS: No light perception • Normal fundoscopy	• MRI: No optic nerve enhancement, CN VII and VIII enhancement • LP: 16% lymphoblasts. Predominant population of TdT+, cCD79a+ B-cell lymphoblasts
Present case	• Chronic, progressive, painless, and bilateral asymmetric (left worse than right) central vision loss • OD: 20/25 • OS: Counting fingers with a left relative afferent pupillary defect • Fundus exam: Bilateral optic nerve pallor	• Initial studies negative • Brain MRI: Negative • LP: No pleocytosis or blasts Follow-up studies showed: • Brain MRI showed enhancement of the left optic nerve, and bilateral sheath enhancement was suspected • Spinal MRI: Enhancement and thickening of the nerve roots of the cauda equina • LP: Lymphocytic predominant pleocytosis with rare blasts

MRI, magnetic resonance imaging; LP, lumbar puncture; BM, bone marrow examination.