Re: Guy et al.: Gene therapy for Leber hereditary optic neuropathy: low-and medium-dose visual results
(Ophthalmology. 2017;124:1621-1634)

TO THE EDITOR: We read with interest the article by Guy et al1 about gene therapy by intravitreous, monocular injection of the AAV2-P1ND4v2 vector carrying the wild-type ND4 gene in 14 patients with Leber hereditary optic neuropathy (LHON) owing to the variant m.11778G>A in the ND4 gene. We have the following comments and concerns.

The main disadvantage of the study is the assumption that LHON only affects the optic nerve and the retinal ganglion cells. Although LHON often presents as a single-organ disease, it is in fact a multiorgan disease, which becomes evident only after years or after prospective investigations of organs other than the optic nerve and the retina. It is meanwhile well-established that LHON not only manifests in the eye and optic nerve but may affect other organs and tissues as well, resulting in a more widespread clinical presentation. Other organs and tissues affected in LHON include the central nervous system (brain [multiple sclerosis–like white matter lesions], the spinal cord [diffuse demyelinating lesions of the thoracic spine]), the ears (hypoacusis), the endocrine organs (diabetes, hyperthyroidism), the heart (noncompaction),2 the kidneys (renal insufficiency), the peripheral nervous system (neuropathy),3 the bone marrow (anemia), the vascular system (arterial hypertension, hyperlipidemia), or the spinal column (kyphosis). How to explain that injection of the vector into a single eye should have a beneficial effect on these more distant tissues? Is it conceivable that tingling in legs, numbness of feet, and headache were in fact manifestations of organ involvement other than the eyes or the genetic effect? Did patients with sensory disturbances undergo nerve conduction studies? What were the results?

A further objection is that spontaneous remission of visual acuity in LHON patients carrying any of the 3 primary variants has been reported.4 Among the primary LHON mutations, it is particularly the m.11778G>A variant that is associated with a favorable outcome if no further secondary mutations are present.1 In the study from Leo-Kottler et al.,5 vision improved spontaneously in all 12 included patients carrying the m.11778G>A variant. Did the authors look for secondary LHON mutations in their 14 patients? How many of them had secondary LHON mutations and which mutations were found? How can the authors exclude the possibility that the presumed therapeutic effect was in fact attributable to spontaneous partial recovery? Did they observe improvement of vision among those who were not injected in either of the 2 eyes, or in the fellow eye among those who were injected? Spontaneous recovery seems to have occurred at least in patients 14 (4>63), 9 (6>9), 5 (20>39), and patient 4 (hand movements >4).

Of the 14 included patients 4 were females and 10 males.1 Because the course of LHON may be at variance between men and women, we should be informed if course and outcome were different between the genders in the injected eye and noninjected eye. There is hardly spontaneous recovery in female patients carrying any of the 3 primary LHON mutations] and female patients have a higher risk of white matter lesions than male patients.3

Overall, this interesting therapeutic study should consider that LHON is in fact a multiorgan disease, that the course may be different between the genders, that it is unclear if gene therapy could reach organs distal to the eyes, and that spontaneous remission, particularly in male m.11778G>A carriers, should be considered as cause of the improvement.

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References