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Research Article

Consider Non-Myasthenic Neuromuscular Disorders as Major Causes of Diplopia

Finsterer J, MD, PhD

[1]Klinik Landstrasse, Messerli Institute, Vienna, Austria

*Corresponding Author
Finsterer J, MD, PhD

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Abstract:

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LETTER TO THE EDITOR

With interest we read the review article by Margolin E. (2020) about the causes, work-up, and treatment options of diplopia (double vision) (Margolin E. 2020). Diplopia may be due to affection of one or both eyes. Diplopia may be permanent or transient. The author concluded that "careful history taking and basic examination skills described in the article should allow a neurologist to make an accurate diagnosis in most cases" (Margolin E. 2020). We have the following comments and concerns.

The main shortcoming of the study is that a number of disorders manifesting with diplopia were not included in this review. The most prevalent among these disorders is myopathy of extra-ocular muscle. Myopathy is a major differential diagnosis of diplopia, which may or may not be associated with concomitant ptosis. Diplopia may occur in primary (genetic) and secondary (acquired) myopathies.

Among the muscular dystrophies, diplopia has been particularly reported in myotonic dystrophy (Thiriez, C. *et al.*, 2010) and oculo-pharyngeal muscular dystrophy (Goyal, N. A. *et al.*, 2019). Among the congenital myopathies diplopia has been most frequently described in nemaline myopathy (Kanatani, M. *et al.*, 2020). The most prevalent myopathic cause of diplopia is metabolic myopathy. Among the metabolic myopathies, double vision is a hallmark of mitochondrial disorders (MIDs). Diplopia occurs in syndromic and non-syndromic MIDs. Among the syndromic MIDs, diplopia occurs most frequently in patients with progressive external ophthalmoplegia (PEO), which may be due to single or multiple mtDNA deletions, mtDNA depletion, or due to point mutations in nDNA or mtDNA located genes encoding for mitochondrial proteins. Diplopia is also a frequent feature of Kearns-Sayre syndrome or Leigh syndrome. Among the hereditary transmission disorders (congenital myasthenic syndromes) diplopia has been reported in patients carrying rapsyn mutations (Yasaki, E. *et al.*, 2004). Among the channelopathies. paramyotonia congenita may manifest with double vision.

Among the secondary myopathies diplopia may occur in sarcoid orbital myopathy (Vahdani, K., & Rose, G. E. 2020). Double vision may be a dominant manifestation of oculomotor, ocular neuromyotonia (Padungkiatsagul, T. *et al.*, 2018). Double vision can be a manifestation of drug-induced myopathy, such as PD-1 myopathy which is due to programmed death inhibitors (Liewluck, T. *et al.*, 2018). Other drugs causing diplopia include tremelimumab, durvalumab (Carrera, W. *et al.*, 2017), or isotrenoin.

Various subtypes of Guillain-Barre syndrome (GBS), particularly Miller- Fisher syndrome (MFS) may manifest with double vision. More rarely, acute, inflammatory, demyelinating polyneuropathy (AIDP), acute, motor, axonal

neuropathy (AMAN), or Bickerstaff encephalitis may manifest with double vision. Diplopia may be a manifestation of neuroborreliosis. Not to forget, thiamine deficiency, manifesting as Wernicke encephalopathy or beri beri, may present with double vision among other typical manifestations (Tan, T. X. Z. *et al.*, 2019).

The author also did not consider double vision due to orbital compartment syndrome due to carotid cavernous fistula. Primary or secondary orbital tumours should be also considered as rare causes of diplopia. Neurologist and ophthalmologist should also consider benign or malign neoplasms of the cerebrum as causes of diplopia. Diplopia has been particularly reported in association with pituitary adenoma, but also in association with lipoma or lymphoma.

Overall, work-up for diplopia should include search for primary and secondary myopathy, for immune-mediated neuropathies, for thiamine deficiency, benign and malign neoplasms, traumatic brain injury, and for orbital tumours. Work-up for these neglected causes of diplopia is crucial as some of them respond favourable to treatment. Early treatment may result in a better outcome than delayed application of treatment.

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