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The Spectrum of Psycho-Ophthalmologic Disorders is Broader and Better Documented than Anticipated

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LETTER TO THE EDITOR

We read with interest Kiely, *et al*'s. review article on congenital or inherited disorders with psychiatric and ophthalmologic disorders (psycho-ophthalmic disorders) [Kiely, C. *et al*., 2023]. Psycho-ophthalmic disorders discussed in the review included Noonan syndrome, Down syndrome, retinitis pigmentosa / Usher syndrome, Susac syndrome, Norrie disease, cerebrotendineous xanthomatosis, Kearns-Sayre syndrome, Wolfram syndrome, neuronal ceroid lipufuscinosis (Batten disease), and Lowe syndrome (oculo-cerebro-retinal syndrome) [Kiely, C. *et al*., 2023]. It has been concluded that various genetic disorders may affect cortical areas relevant to visual processing and therefore may affect eye-brain connections [Kiely, C. *et al*., 2023]. The study is impressive, but some points require discussion.

The major limitation of the study is that the PubMed search conducted for the review only covered the period October 2021 to July 2022 [Kiely, C. *et al*., 2023]. In such a short period of time, significant literature contributions on this topic may be missed. Another limitation is that only three keywords were used for the literature search, which also poses the risk that a number of papers were not included in the review. We should know the reason why such a short period of time was screened for suitable articles and why only three search terms were applied.

One consequence of the limited literature search could be that the phenomenon of stroke-like episodes (SLEs) was not addressed. SLEs are the pathognomonic phenotypic feature of mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome. Among other features, SLEs often manifest with visual impairment, confusion [Ihara, M. *et al*., 1996], and even psychosis [Iizuka, T. *et al*., 2003]. SLEs occur not only in MELAS but also in various other primary (genetic) mitochondrial disorders and are often confused with ischemic stroke. However, the imaging characteristics of SLEs are unique and significantly different from those of ischemic stroke. MELAS is due to the *MT-TL1* variant m.3243A>G in approximately 80% of cases.

Another primary mitochondrial disorder not covered in the review is neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome. NARP syndrome is due to near-homoplasmic variants in *MT-ATP6*. NARP not only has the canonical features neuropathy, proximal muscle weakness, cerebellar ataxia and retinitis pigmentosa, but can also be a multisystem disease: Non-canonical features of NARP include epilepsy, cerebral or cerebellar atrophy, optic atrophy, cognitive impairment, dementia, sleep apnea syndrome, hearing impairment, renal failure, and diabetes [Finsterer, J, 2023]. In addition, individual patients with NARP and psychosis have also been reported.

Missing from the overview are hereditary autism spectrum disorders (ASDs). Psycho-ophthalmic abnormalities may be present, particularly when autism is associated with multisystem disease. An example is Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome, a newly described autosomal dominant multisystem developmental disorder resulting from mutations in *SON* [Eid, M. *et al*., 2022]. ZTTK is clinically characterized by mental retardation, facial dysmorphism, poor feeding, visual impairment, musculoskeletal abnormalities, congenital defects of heart and genitourinary system, seizures, tone abnormalities, ASD and variable morphologic brain abnormalities [Eid, M . *et al*., 2022]. Another example is ASD with optic atrophy due to variants in *WDR45*. There is also no mention of Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS), a rare neurodevelopmental disorder characterized by visual impairment, intellectual disability, and autistic features due to variants in *NR2F1*. Several other ASDs with psycho-ophthalmic features should have been discussed (e.g. Senior Løken syndrome due to

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SLCT1 variants, ASD due to *ATP1A3* variants, Leber's hereditary optic neuropathy).

Numerous other genetic psycho-ophthalmic phenotypes require discussion in a review with the aims defined as in the index review (e.g. hereditary spastic paraplegia type-7, 3q29 deletion syndrome, 3q27.3 microdeletion syndrome, Mohr Tranebjaerg syndrome)

It is incomprehensible why two paragraphs on non-hereditary, non-congenital conditions were included in the discussion at the end of the review ("retinal findings in psychiatric disorders", "disentangling mental health disorders from visual impairments"). These two paragraphs are outside the scope of the review and should therefore be excluded.

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. The spectrum of hereditary psycho-ophthalmic disease is much broader than discussed. The low prevalence of psycho-ophthalmic disorders should not be the reason not to discuss them.

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