

The eye as a window to the brain

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Over the last 20 years, it has become evident that the age-old expression, “the eye is the window into the soul”, might in fact hold more truth than previously thought. We are currently able to distinguish a variety of systemic diseases by funduscopy inspection. Following the dawn of high-resolution optical coherence tomography (OCT), we are now capable of supporting the diagnoses of demyelinating diseases by retinal nerve fibre layer and ganglion cell layer analysis—one of the many capabilities of this technique. This begs the question: what are the limits of our ability to peer into the eye to inform us of diseases elsewhere in the central nervous system? This question has more relevance today than ever, lending appreciation to the efforts of Sathianvichitr et al. and the thrust of the team’s work¹ published in this issue of the *Annals*.

Our ability to forestall neurodegenerative diseases depends greatly on techniques to detect them in the presymptomatic stage. With the development of new, potentially effective therapies to prevent progression of the inexorable cognitive decline that characterises Alzheimer’s disease (AD),² tests to diagnose the disease as early as possible are urgently needed. Early diagnosis of AD is a tall order. Thus far, to diagnose AD, we have principally relied on historical information provided by patients and their relatives, as well as a clinical cognitive examination. Newer neuroimaging techniques³ and gene analysis⁴ add to the neurologist’s diagnostic acumen as important tools in early diagnosis.

The desperate need to devise non-invasive and sensitive tests for the diagnosis of AD was best illustrated by a salvo of interest in the pupil response to light as a means to enhance the diagnostic acumen of the neurologist. This effort reached a feverish pitch in the 1990s. In 1994, Scinto et al. at Harvard University, Cambridge, US published a study that reported the pupil response to eye drops in AD-affected individuals compared to normal individuals.⁵ They stated that hypersensitivity of pupil dilation to topical instillation of the cholinergic antagonist tropicamide was a marker of disease in AD, adding that this could be used clinically in its diagnosis. The hypothesis stated that the pupil

response to light in AD patients was heightened. Unfortunately, the study never led to concrete or useful diagnostic findings, although the pupil as a biomarker in AD continues to be a source of keen interest.

Many other valiant efforts to diagnose AD in the early stage have come and gone, though not without having imparted important lessons. Those which pertain to the visual pathways are briefly mentioned here. The individuals with the so-called posterior variant of AD—also known as posterior cortical atrophy—will often exhibit clinical features, which herald the better-known language and memory disorders that more saliently characterise AD. A post-chiasmal visual field defect accompanied by simultanagnosia and alexia could be the earliest manifestations of AD.⁶ Following many publications that have underscored this less common AD variant, colleagues in the field of neuro-ophthalmology are positioned to provide assistance to those in the field of neuro-cognition to recognise early AD. However, there is indeed a small percentage of patients with early AD—that is, those with the posterior cortical atrophy variant of AD.

As part of continuing efforts⁷ to find new and useful application of funduscopy examination to diagnose central nervous system diseases, Sathianvichitr et al.¹ have reviewed techniques of artificial intelligence (AI) and its application in the tricky world of early diagnosis of AD. Their study delves into the complex world of AD—a world already filled with hundreds of promising hypotheses and brilliant ideas, though without clear immediate application in early diagnosis so far. This lack of established pathways to obvious applications is one difficulty in advancing early detection of neurodegenerative diseases, despite great efforts in studying AD overall. In the review of AI and deep learning (DL), the team, comprising well-established investigators in the domain of AI and DL, attempted to recognise diseases which have manifestations in the ocular fundus. The researchers zero in on a topic with considerable history—that is, the detection of neurodegenerative diseases by retinal examination. They reviewed studies which have identified patients

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with AD whose features can be discriminated from cognitively normal individuals, using AI applied to retinal images.

The methods used to feed data into a DL database are well understood. The algorithms by which the DL “machine” learns and solves a problem are less so. We do know that DL uses AI methods; retrospectively, these methods have been said to be able to identify sex, age, presence of glaucoma, papilloedema and hypertension, to mention a few recognisable characteristics. How DL identifies sex is less clear, but this is of great interest. Furthermore, age determination based on fundus photography examination remains an unknown. A fundamental mystery is how a database that is entered into an AI context goes the step further to recognise features not identifiable to an experienced ophthalmologist, which when solved will yield remarkable new findings with far-reaching consequences. Much better understood are ways in which DL might solve queries for glaucoma or papilloedema.

How to transit from methods which allow DL to recognise the optic nerve pathology, to methods which allow DL to recognise features of AD patients on OCT is an exceedingly important question. Thinning of the retinal nerve fibre layer or vascular changes might provide an answer. The presence of patterns of atrophy not noted by funduscopy or the trained eye may be an additional possibility. The recognition of patterns of thinning or thickening of deep retinal or choroid vessels might also be considered. Atrophy or segmental atrophy of various retinal layers might eventually turn out to be the answer; after all, patients with advanced AD

have brain atrophy. Thus, why not the retinal nerve fibre layer?

The review by Sathianvichitr et al. is a tour de force of all the efforts currently underway in using DL methods to diagnose and discriminate AD from normal age-matched individuals. The critical question is whether the race for the diagnosis of AD will be propelled by funduscopy analysis (of any type) or the discovery of a spinal fluid marker. With the view that patients in later stages of AD lose their memory and even their personality—that is, arguably their soul—peering into the eyes in search of solutions to the problem of ageing with dementia has never acquired greater relevance.

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