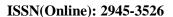
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Letter to the Editor

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Before Attributing the Unilateral Adie's Pupil to SARS-CoV-2 Infection, Alternative Causes Must Be Ruled out and the Pathophysiology Explained

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LETTER TO THE EDITOR

We read with interest the article by Cakir *et al.* about a 28-year-old woman who was diagnosed with a unilateral Adie's pupil two months after a mild SARS-CoV-2 infection (SC2I) [Çakır, G. Y. *et al.*, 2024]. The left enlarged pupil did not respond to light and convergence, but responded promptly to pilocarpine [Çakır, G. Y. *et al.*, 2024]. Adie's pupil recovered only incompletely at the one-year follow-up [Çakır, G. Y. *et al.*, 2024]. The study is noteworthy, but several points should be discussed.

The first point is that the patient was not referred to a neurology service [Çakır, G. Y. et al., 2024]. As the patient had headaches and anosmia during the course of SC2I [Çakır, G. Y. et al., 2024], it would have been imperative to rule out central nervous system (CNS) disease and neuropathy of the cranial nerves, particularly cranial nerve I and III. As the D-dimer was significantly elevated during SC2I, it would have been particularly important to rule out venous sinus thrombosis (VST), which has been reported as a complication of SC2I [Bregel, L. V. et al., 2023]. The pathophysiology of VST associated with SC2I could be explained by the development of PF4 antibodies against surface markers on platelets [Yang, C. et al., 2024]. Were PF4 antibodies elevated in the index patient?

The second point is that the temporal relationship between the onset of Adie's pupil and SC2I does not exclude the possibility that Adie's pupil was due to causes other than SC2I. Therefore, we should know if there was a history of head trauma, migraine, viral infections other than SC2I (e.g. herpes simplex, herpes zoster, measles, mumps) or bacterial infections (e.g. cat scratch fever, Lyme disease, syphilis).

The third point is that meningitis/encephalitis cannot be ruled out as a differential cause of Adie's pupil [Çakır, G. Y. *et al.*, 2024]. To rule out infectious or immunologic meningitis/encephalitis,

MRI with contrast, CSF studies, CSF viral panels, CSF cultures, and determination of antibodies related to autoimmune encephalitis would have been essential.

The fourth point is that the family history was not reported [Çakır, G. Y. *et al.*, 2024]. Since Adie's syndrome may be hereditary [Andre-van Leeuwen, M. *et al.*, 1946], it would have been imperative to obtain a thorough family history and possibly examine other first-degree family members.

The fifth point is that Adie's pupil could be pathophysiologically explained by cerebrovascular disease [Hoang, T. T. *et al.*, 2021]. Therefore, it would have been important to rule out cerebral ischemia and especially cerebral vasculitis by computed tomography angiography (CTA) and to determine the serum parameters of vasculitis.

The sixth point is that it was not stated whether the patient had only Adie's pupil or also Adie's syndrome. The latter is characterized not only by Adie's pupil but also by ataxia and reduced or absent deep tendon reflexes. Were these additional features present in the index patient?

The seventh point refers to the statement that "Adie's pupil is also known as Adie's syndrome" [Çakır, G. Y. *et al.*, 2024]. These are two different entities that need to be carefully distinguished.

To summarize, this interesting study has limitations that put the results and their interpretation into perspective. Removing these limitations could strengthen the conclusions and reinforce the message of the study. All unanswered questions need to be addressed before readers can uncritically accept the study's conclusions. Before attributing unilateral Adie's pupil to SC2I, alternative causes must be ruled out and the pathophysiology explained.

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