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Adie's Pupil: A Diagnostic Challenge for the Physician

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Adie's pupil, also called tonic pupil, is mainly seen in young women. Most patients have unilateral eye involvement. The pupil of the affected side is significantly larger than that on the healthy side. The direct and indirect light reflection from the pupil on the affected side disappears. The pupil on the affected side is sensitive to low concentrations of pilocarpine. The pathogeneses of Adie's pupil are complex, some of which are insidious and lack corresponding specific diseases. Through a literature review, we found that Adie's pupil is mainly associated with infectious diseases, most commonly syphilis, followed by immune diseases and paraneoplastic syndromes. The ophthalmological symptoms and pupil abnormalities can disappear after active treatment of the primary disease. Pilocarpine can be used to treat ophthalmologic symptoms, such as blurred vision, for which patients might visit an ophthalmologist or neurologist. It is essential for clinicians to improve their understanding of the disease to avoid misdiagnosis. Differential diagnosis between Adie's pupil, oculomotor nerve palsy, anticholinergic drug overdose, Argyll-Robertson pupil, and congenital mydriasis need to be identified by the physician. Here, the clinical manifestations, pathogenesis, relationship between Adie's pupil and diseases, and differential diagnosis of Adie's pupil are reviewed.

Keywords: **Pilocarpine • Pupil Disorders • Vision Disorders**

Abbreviations: **AAG** – autoimmune autonomic ganglionopathy; **AIDS** – acquired immunodeficiency syndrome; **CIDP** – chronic inflammatory demyelinating polyneuropathy; **COVID-19** – coronavirus disease 2019; **GBS** – Guillain-Barre syndrome; **IVIg** – intravenous immunoglobulin; **IVMP** – intravenous methylprednisolone; **MFS** – Miller Fisher syndrome; **VKH syndrome** – Vogt-Koyanagi-Harada syndrome

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Background

The size of the pupil is adjusted by the pupillary sphincter and dilator. The contraction of the pupillary sphincter muscle when innervated by the parasympathetic nerve fibers shrinks the pupil. However, the contraction of the pupillary dilator muscle when innervated by the sympathetic nerve fibers dilates the pupil [1]. There are 2 types of pupil reflection. The first is the light reflex, which causes bilateral pupils to shrink when 1 pupil is illuminated; the second is the accommodative reflex, also known as the near reflex, which is manifested by the bilateral pupil constriction when staring at a nearby object [2].

Adie's pupil, also called tonic pupil, was first reported by the British neurologist William John Adie in 1931 [3]. It manifests as unilateral or bilateral pupil dilation, direct and indirect loss or weakening of light reflection, abnormal adjustment reflex, and pupil contraction disorder. Adie's pupil is predominantly seen in young women, with an age of onset of 20 to 40 years. Patients usually observe that 1 pupil is larger than the other when looking in the mirror. Unilateral involvement is observed in 80% of patients [4]. Adie's pupil usually exists in isolation, but it should be noted that it can be associated with other symptoms or can be part of other symptoms. When it is accompanied by weakening or disappearance of deep reflexes, it is known as Adie syndrome or Holmes-Adie syndrome [5]. When Adie's pupil is accompanied by weakened or absent deep reflexes and segmental anhidrosis, it is known as Ross syndrome [6]. The complexity of the pathogenesis often leads to difficulty in identifying Adie's pupil and possible related diseases by ophthalmologists and neurologists.

Survey Methodology

In this review, we used PubMed, Scopus, Web of Science, and Google Scholar to collect case reports of Adie's pupil from 2010 to 2020 (**Table 1**) [7-42]. In the reports found, women accounted for 62.5% (25/40), and men accounted for 37.5% (15/40) of cases. The main symptoms of patients were blurred vision (65%, 26/40), photophobia (15%, 6/40), diplopia (12.5%, 5/40), and pain behind the eyeball (5%, 2/40). Some patients experienced no ophthalmologic symptoms (30%, 12/40).

Clinical Manifestations of Adie's Pupil

The characteristics of Adie's pupil can be summarized as follows: the affected pupil is significantly larger than the normal pupil; the direct and indirect reflection of light from the affected pupil disappears; and the affected pupil is sensitive to low concentrations of pilocarpine (**Figure 1**).

Pathogenesis of Adie's Pupil

Adie's pupil is usually secondary to eye diseases, including infections, tumors, autoimmune diseases, and trauma; however, it can also be associated with systemic diseases with autonomic dysfunction. It is generally considered a peripheral neuropathy caused by damage to the ciliary ganglion and its parasympathetic postganglionic fibers [3]. The ciliary ganglion contains fibers that innervate the ciliary muscle (responsible for adjusting the lens) and the pupillary sphincter. The number of fibers that innervate the ciliary muscle far exceed those that innervate the pupillary sphincter. Thus, when the ciliary ganglion is damaged, the fibers innervating the ciliary muscles have a greater chance of survival. This causes the fibers that originally innervated the ciliary muscles to innervate the pupillary sphincter [40]. Compared with normal pupil fiber regeneration, this abnormal regeneration leads to pupillary contraction and abnormal accommodation.

Relationship Between Adie's Pupil and Diseases

Through the literature review, we found that Adie's pupils are mainly associated with infectious diseases, most commonly syphilis, followed by immune diseases and paraneoplastic syndromes (**Table 1**). On encountering Adie's pupils, the first disease that needs to be ruled out is syphilis, followed by other diseases, such as Vogt-Koyanagi-Harada syndrome and Sjogren syndrome, and other infections, autoimmune diseases, and paraneoplastic syndromes (**Figure 2**). The ophthalmologic symptoms and pupil abnormalities can disappear after treatment of the primary disease. A diagnosis of idiopathic Adie's pupil can be considered after exclusion of all possible primary diseases. Pilocarpine can be used to treat ophthalmologic symptoms, such as blurred vision [40].

Differential Diagnosis of Adie's Pupil

Adie's pupil needs to be distinguished from pupil abnormalities caused by the following factors:

Oculomotor nerve palsy: In addition to the dilated pupils and loss of light reflection, there are other clinical manifestations, such as ptosis and restricted eye movements. Brain magnetic resonance imaging can reveal damage to the oculomotor nerve nucleus and fibers [43], and the pilocarpine test is usually negative [44].

Drug overdose: Atropine is an anticholinergic drug that can lead to a series of anticholinergic symptoms after excessive intake, including dilated pupils, hallucinations, agitation, tachycardia,

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Table 1. Literature review of Adie's pupil cases from 2010 to 2020.

Literature review	Sex/age	Clinical manifestations	Unilateral/ bilateral	Response to dilute pilocarpine	Accompanied disease	Treatment
Takata [7]	Male/30	Blurred vision	Left	Left pupil constriction (0.125%)	Neurosyphilis	Penicillin G
Camoriano [8]	Male/39	Blurred vision	Right	Right pupil constriction (0.125%)	Neurosyphilis	Penicillin G
Jivraj [9]	Female/38	Blurred vision	Bilateral	Bilateral pupil constriction (0.1%)	Neurosyphilis	Penicillin G
Rissardo [10]	Male/23	Blurred vision	Left	NA	Neurosyphilis	Penicillin G
Gu [11]	Male/41	Blurred vision	Left	Left pupil constriction (0.5%)	Neurosyphilis	Ceftriaxone
Pecero-Hormigo [12]	Male/33	Blurred vision	Right	NA	Neurosyphilis	Penicillin G
Reyes [13]	Male/30	No	Bilateral	Bilateral pupil constriction (0.125%)	Neurosyphilis AIDS	Penicillin G
Cerny [14]	Female/38	Blurred vision, pain behind the eyeball, photophobia	Bilateral	Bilateral pupil constriction (0.1%)	AIDS	Tenofovir
Ortiz-Seller [15]	Female/51	Blurred vision, pain behind the eyeball	Bilateral	Bilateral pupil constriction (0.1%)	COVID-19	Oral prednisone
Ordás [16]	Male/62	Blurred vision, diplopia	Left	Left pupil constriction (0.125%)	COVID-19	Oral prednisone
Karadžić [17]	Female/59	Blurred vision	Left	Left pupil constriction (0.125%)	Viral hepatitis	NA
Karadžić [17]	Female/55	No	Left	Left pupil constriction (0.125%)	Viral hepatitis	NA
Lana-Peixoto [18]	Female/33	No	Left	Left pupil constriction (0.1%)	Leprosy	NA
Lana-Peixoto [18]	Female/42	No	Bilateral	Bilateral pupil constriction (0.1%)	Leprosy	Steroid, anti-leprosy drugs
Bhagwan [19]	Female/35	Blurred vision, redness of both eyes	Bilateral	Bilateral pupil constriction (0.1%)	Sjogren syndrome	NA
Bhagwan [19]	Female/45	Blurred vision	Bilateral	Bilateral pupil constriction (0.1%)	Sjogren syndrome	IVIg
Miranda [20]	Female/51	No	Right	Right pupil constriction (0.125%)	Sjogren syndrome	NA
Robles-Cedeño [21]	Female/23	Blurred vision, diplopia, photophobia	Bilateral	Bilateral pupil constriction (0.125%)	VKH syndrome	Steroid

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Table 1 continued. Literature review of Adie's pupil cases from 2010 to 2020.

Literature review	Sex/age	Clinical manifestations	Unilateral/ bilateral	Response to dilute pilocarpine	Accompanied disease	Treatment
Narang [22]	Male/28	Blurred vision	Bilateral	Bilateral pupil constriction (0.16%)	VKH syndrome	IVMP
Garza [23]	Female/37	Blurred vision, redness of both eyes	Bilateral	Bilateral pupil constriction (0.16%)	VKH syndrome	Prednisolone, tropicamide-phenylephrine, betamethasone
Sevketoglu [24]	Male/5	No	Left	Left pupil constriction (0.125%)	GBS	Plasmapheresis, IVIg
Escorcio-Bezerra [25]	Female/23	Blurred vision, diplopia	Bilateral	Bilateral pupil constriction (0.125%)	CIDP	Plasmapheresis, corticoids
Matalia [26]	Female/16	Blurred vision	Right	Right pupil constriction (0.125%)	Takayasu arteritis	NA
Kaymakamzade [27]	Male/17	Diplopia	NA	NA	MFS	IVIg
Kaymakamzade [27]	Male/66	Diplopia	Bilateral	Bilateral pupil constriction (0.125%)	MFS	IVIg
Morimoto [28]	Female/42	Photophobia	Left	Left pupil constriction (0.125%)	AAG	IVIg, IVMP
Peyman [29]	Female/45	Blurred vision photophobia	Left	Left pupil constriction (0.1%)	Breast cancer	NA
Srinivasan [30]	Male/7	No	Bilateral	Bilateral pupil constriction (0.125%)	Hodgkin lymphoma	Chemotherapy
Horta [31]	Male/48	No	Left	NA	Hodgkin lymphoma	Chemotherapy
Zhang [32]	Female/50	No	Right	Right pupil constriction (0.0625%)	Mediastinal small cell carcinoma	Chemotherapy
Yamane [33]	Female/50	Blurred vision	Left	Left pupil constriction (0.125%)	Adenoid cystic carcinoma	NA
Han [34]	Female/36	Blurred vision	Bilateral	Bilateral pupil constriction (0.125%)	Dorsal midbrain syndrome	Surgery
Kim [35]	Female/2	No	Left	Left pupil constriction (0.1%)	Inferior oblique myectomy	NA
Babiano [36]	Male/NA	No	Right	Right pupil constriction (0.125%)	Traumatic brain injury	NA
Tafakhori [37]	Female/27	Blurred vision	Left	Left pupil constriction (0.125%)	Migraine	Pilocarpine (0.125%)

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Table 1 continued. Literature review of Adie's pupil cases from 2010 to 2020.

Literature review	Sex/age	Clinical manifestations	Unilateral/ bilateral	Response to dilute pilocarpine	Accompanied disease	Treatment
Garrick [38]	Female/22	No	NA	Pupil constriction	Dysautonomia	IVIg
Colak [39]	Female/31	Blurred vision	Left	Left pupil constriction (0.5%)	No	NA
Batawi [40]	Male/40	Blurred vision, photophobia	Right	Right pupil constriction (0.1%)	No	Pilocarpine (1%)
Durán-Ferreras [41]	Female/16	Blurred vision	Right	Right pupil constriction (0.125%)	No	NA
Rivero Rodríguez [42]	Female/21	Blurred vision, photophobia	Left	Left pupil constriction (0.125%)	No	NA

NA – not available; AAG – autoimmune autonomic ganglionopathy; AIDS – acquired immunodeficiency syndrome; CIDP – chronic inflammatory demyelinating polyneuropathy; COVID-19 – coronavirus disease 2019; GBS – Guillain-Barre syndrome; IVIg – intravenous immunoglobulin; IVMP – intravenous methylprednisolone; MFS – Miller Fisher syndrome; VKH syndrome – Vogt-Koyanagi-Harada syndrome.

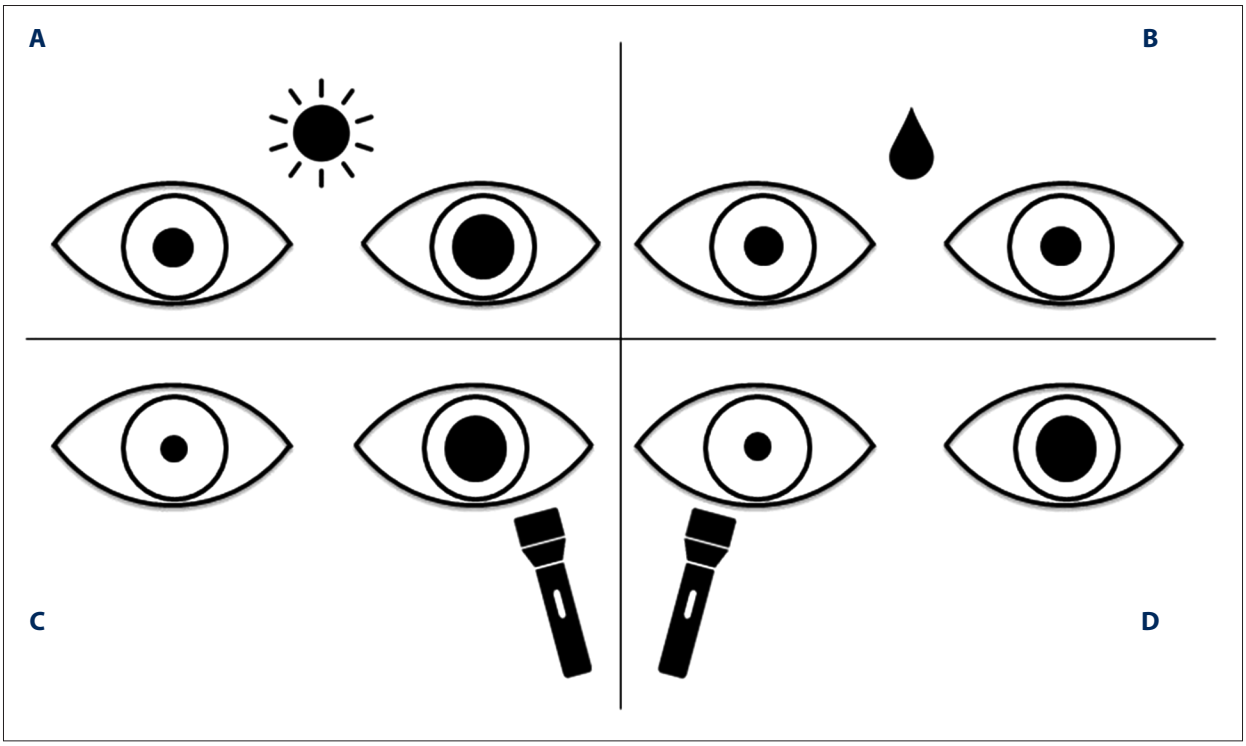

Figure 1. The characteristics of Adie's pupils. (**A**) Under natural light, the pupil on the left is significantly larger than the pupil on the right. (**B**) After 0.125% pilocarpine is applied in both eyes, the left pupil shows obvious contraction; however, the right pupil remains unchanged. (**C**) On exposure of the left pupil to a flashlight, it remains unchanged, while the right pupil contracts significantly; that is, the direct reflection of light from the left pupil is absent, and the indirect reflection from the right pupil exists. (**D**) On exposure of the right pupil to the flashlight, it contracts significantly, while the left pupil does not change; that is, direct reflection of light from the right pupil exists, and indirect reflection from the left pupil is absent. The sun symbol represents natural light; the water drop symbol represents the use of pilocarpine applied in the eyes; the flashlight symbol represents the light reflection from the pupil.

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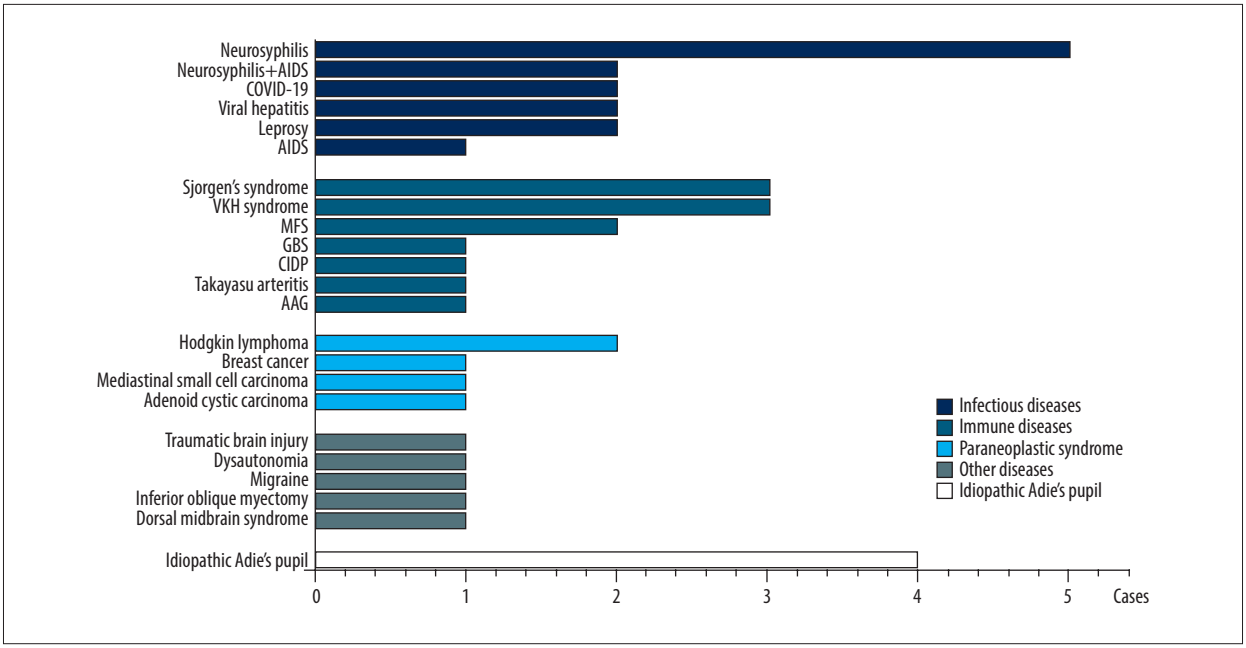

Figure 2. The disease spectrum of Adie's pupil. AAG – autoimmune autonomic ganglionopathy; AIDS – acquired immunodeficiency syndrome; CIDP – chronic inflammatory demyelinating polyneuropathy; COVID-19 – coronavirus disease 2019; GBS – Guillain-Barre syndrome; IVIg – intravenous immunoglobulin; IVMP – intravenous methylprednisolone; MFS – Miller Fisher syndrome; VKH syndrome – Vogt-Koyanagi-Harada syndrome.

delirium, and fever [45]. In addition, Datura, a traditional Chinese medicine, can also cause the above symptoms when ingested in large quantities [46].

Argyll-Robertson pupil: It is generally thought to be related to neurosyphilis. Patients usually present with bilateral miosis, loss of direct and indirect light reflection, and presence of accommodation and convergence reflexes. The affected pupil dilates after atropine instillation [47].

Congenital mydriasis: Mydriasis and associated loss of light reflex are congenital, and both pupils can be affected. It is more common in women, and the pathogenesis is unclear. A combination of medical history and negative pilocarpine test can assist in identification of congenital mydriasis [48].

Conclusions

Adie's pupil demonstrates sex predilection, having a greater incidence in women than men. Blurred vision is the main clinical manifestation of this disease. However, some patients have no ophthalmologic symptoms. The characteristics of Adie's pupil can be summarized as follows: the affected pupil is significantly larger than the normal pupil; the direct and indirect reflection of light from the affected pupil disappears; and the affected pupil is sensitive to low concentrations of pilocarpine. Adie's pupil is mainly associated with infectious diseases, most commonly syphilis, followed by immune diseases and paraneoplastic syndromes. After active treatment of the primary disease, the ophthalmologic symptoms and pupil abnormalities can disappear. Pilocarpine can be used to treat ophthalmic symptoms, such as blurred vision. Differential diagnosis between Adie's pupil, oculomotor nerve palsy, anticholinergic drug overdose, Argyll-Robertson pupil, and congenital mydriasis need to be identified by the physician. Therefore, when evaluating patients with manifestations similar to Adie's pupil, physicians should first identify the diseases mentioned above. Low concentrations of pilocarpine, detailed history, and physical examination can be helpful. The primary disease spectrum behind Adie's pupil should be actively screened.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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