



# History of Ophthalmology

## William John Adie: the man behind the syndrome

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### ABSTRACT

William John Adie was an Australian neurologist in the early 20th century responsible for extensively describing the tonically dilated pupil associated with absent deep tendon reflexes – both features of a syndrome that now bears his name. In addition to other neurological syndromes, he was also significant in delineating narcolepsy through his clinical essays and case series. His ophthalmic and neurologic contributions have served the test of time and played an important role in the modern understanding of Adie syndrome and narcolepsy. This report reviews Adie's medical contributions, extensive descriptions of Adie syndrome, and provides a brief biographical account of his life.

**Key words:** William John Adie, Adie syndrome, Adie pupil, Australia, neuro-ophthalmologist.

### INTRODUCTION

William John Adie, MEd, FRCP, was a busy Australian neurologist who made significant contributions to the scientific community. He is now best known for the slow-moving, dilated pupil that bears his name (i.e., Adie pupil) and for his description of narcolepsy. Despite his considerable contributions to neurology, there is little documentation of Adie's life and work in the medical literature. This report provides some information about Adie's life and offers a current understanding of his contributions.

We have reviewed various papers and other original documents found in the literature and in the archives of the Charing Cross Hospital and Queen Square medical libraries in London. Many of Adie's obituaries were found at the Charing Cross Hospital since he worked there in his final years. He had also spent a number of years at the National Hospital for Neurology and Neurosurgery at Queen Square, which is where his job applications, testimonials supporting his applications and curriculum vitae are stored. The archives of the Association of British Neurologists were also reviewed for information.

### BIOGRAPHY

Originally from Australia, William John Adie, the eldest son of Mr. David Adie, was born in Geelong, a small port city on the southern Australian coast southwest of Melbourne, on 31 October 1886. He began his education at Flinder's School but left at the age of 13 after the death of his father, and started working as an errand boy to support his family. One of his employers recognized his unusual ability and intelligence, and offered to fund his further education at evening classes. This eventually got Adie through his entrance exams and started on his university education.<sup>1–5</sup>

The inspiration to pursue a career in medicine mostly came from a hometown physician named Arthur South. The high cost of medical school attendance in Melbourne led him to move to the United Kingdom. At age 20, with the help of his

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uncle in Boston, Massachusetts, who paid £19 for a one-way ticket to the United Kingdom, and a scholarship, Adie enrolled at University of Edinburgh's MB ChB programme. In addition to being a distinguished student, he made his mark in rowing. Upon further enrolment and completion of his MD degree, he received a gold medal in his final examinations, and for his thesis.<sup>1-5</sup>

In July 1911, after graduating from medical school in Edinburgh, he spent 4 months in further medical education in Boston and New York. He was also awarded the McCosh Graduates scholarship reserved for those with 'professional attainments and ability' and 'knowledge of foreign languages'.<sup>6</sup> This enabled him to gain clinical experience in Berlin, Munich, Vienna and Paris. In October 1911, he worked for 5 months in the 'Krankenhaus links der Isar' clinic with Dr. Gottfried Böhm, who had been an assistant to Dr. Friedrich Müller. After short stints in Paris and Vienna, he settled in Berlin where he worked in Dr. Fedor Krause's clinic. Adie's childhood exposure to the German language from sailors at Geelong port served him well. He also took numerous courses in the Pathology department of the 'Krankenhaus am Urbau' with Dr. Max Koch. He also worked in the bacteriology department of the 'Rudolf Virchow Krankenhaus' with Dr. Liefmann. This is where Adie may have developed his liking for neurology when he became especially interested in the serology of cerebrospinal syphilis and other cerebrospinal fluid-related pathology.<sup>6</sup>

A year later, he returned to Edinburgh to practise for a short period before starting work as a house physician at London's National Hospital for the paralysed and epileptic in Queen Square. Despite attempts by his uncle to bring him back to Australia, Adie's affection for Britain led him to spend the rest of his life there.<sup>1-5</sup>

During World War I, Adie joined the Northamptonshire Regiment and served as a regimental medical officer in France (Fig. 1). He participated in the retreat from Mons, but a well-timed measles infection kept him out of the skirmish in which his battalion was mostly destroyed. He was then dispatched to the Leicestershire Regiment where he actively served for 2 years.<sup>1-5</sup> His innovative ability was evident when in 1916, he was mentioned in various dispatches for saving a number of soldiers in one of the early gas attacks by improvising a mask of clothing soaked in urine.<sup>7</sup>

During a brief leave from the regiment in 1916, he married Lorraine Bonar, a girl he had met in Edinburgh. They soon had two children, a son and a daughter. Eventually, he returned to serve as the neurological specialist to the 7th General Hospital of the British Expeditionary Force and became a consultant to the 2nd Army's Centre for the manage-



**Figure 1.** Captain William John Adie. Royal Army Medical Corps. 1914–1919. *Courtesy of Chesney, Ltd.*

ment of head injuries. During this consultancy at St. Omer, he collected significant volumes of invaluable neurological material that sadly were never published.<sup>1-5</sup>

Upon return from the war, Adie became a medical registrar at Charing Cross Hospital in London. Subsequently, he joined the staffs of the Royal Northern Hospital, National Hospital for Nervous Disease, Queen Square, Mount Vernon Hospital, Northwood and Moorfields Eye Hospital (formerly Royal London Ophthalmic Hospital) where he practised general medicine specializing in neurology. He then became a member of the Royal College of Physicians in 1919. In 1926, Adie was at the apex of his career when he was elected a fellow of the Royal College of Physicians and received a gold medal for his MD at Edinburgh. In 1929, he became the secretary to the Section of Neurology and Psychological Medicine at the Annual Meeting of the British Medical Association (Fig. 2). In 1932, Adie was one of the founders of the Association of British Neurologists, which was formed at a meeting at the house of fellow neurologist Gordon Holmes (Fig. 3). As described by his students and colleagues in his many obituaries, he was a sought-after teacher and a diagnostician with excellent clinical acumen and a compassionate outlook on life.<sup>1-6</sup>

Throughout his life, Adie's character was described as being kind, modest and approachable. His

students held him in high regard and were treated by Adie as colleagues. His life was vigorous and productive. He was a keen ornithologist and tennis player. He was also passionate about skiing and skating during his vacations in Switzerland.<sup>1-5,7</sup>



**Figure 2.** William John Adie, MD FRCP. *Courtesy of the Queen Square Archives and Museum.*

In 1932, at the age of 45, Adie began suffering from angina pectoris. Only 3 years later, he was forced to resign from his work due to his health problems. Later that year, sadly, Adie died at his house in Golders Green, London, from a myocardial infarction on 17 March 1935, at an early age of 48. Many obituaries and letters were written in adulation and admiration of Adie. He was recognized in his hometown's daily newspaper, *Geelong Advertiser*, with a long obituary entitled 'Geelong boy who made good in London'.<sup>1-5</sup>

### ADIE SYNDROME

The pinnacle of his career came when, in 1931, he published in the *British Medical Journal* his observations on a clinical syndrome involving a tonic pupil with diminished or absent deep tendon reflexes.<sup>8</sup> This eventually became known as Adie syndrome or Holmes-Adie syndrome with the hallmark feature of the tonic pupil or Adie pupil.<sup>5</sup>

The most primitive depictions of the tonic pupil came as early as 1813 by James Ware<sup>9-11</sup> and 1881 by Hughlings Jackson.<sup>9,10,12</sup> However, the more cited and recognized written descriptions of tonic pupil came simultaneously in 1902 when Saenger<sup>9,13</sup> and Strasburger<sup>9,14</sup> described it independently. Since then, numerous articles on the tonic pupil have appeared in the medical literature.<sup>9,15</sup> The association of tonic pupils with absent tendon reflexes was first noted by Markus in 1906.<sup>16</sup>

Although not the first to discover this phenomenon, in 1931, Adie was among the first to



**Figure 3.** Group with Greenfield and Adie. 1931. Adie is second from the left, in front row. *Courtesy of the Queen Square Archives and Museum.*

acknowledge the relationship between tonic pupil and deep tendon reflexes by reporting six cases of his own.<sup>8</sup> In 1932, he reported eight more cases and recorded 44 reported cases of such pupils, of which nine reported absent tendon reflexes, in his clinical essay for the *Brain* journal.<sup>17</sup> In this essay, he further elaborated on the syndrome and classified it as 'the presence of the tonic pupillary reaction in its most characteristic form and absence of one or more of the tendon reflexes'.<sup>17</sup> He recognized Saenger's and Strasburger's earlier work from 1902 and gave credit to a number of individuals who had previously recorded cases of similar findings.<sup>17</sup> The clinical essay served to reaffirm the benign nature of the disorder. Importantly, he was among the first to nullify the misconstrued association between the Argyll Robertson pupil of syphilis and the tonic pupil.<sup>17</sup>

Controversy has surrounded the naming of the syndrome since the beginning as many individuals had reported similar findings.<sup>9</sup> It was Adie's dogmatic style, his tireless dedication to the syndrome and the controversies stirred up by his papers that brought it to general attention.<sup>9</sup> This eventually led to the syndrome being recognized as Adie syndrome.

In 1931, around the same time as Adie's first paper on tonic pupils, Gordon Holmes reported 54 cases largely gathered from the literature, in 19 of which tendon reflexes were diminished or absent.<sup>18</sup> This prompted Bramwell,<sup>18</sup> in 1936, to propose Holmes–Adie syndrome as a disease synonym. This is why Adie syndrome is also referred to as Holmes–Adie syndrome.

## Disease classification

Adie outlined two forms of the syndrome, the complete form and incomplete form.<sup>17,19</sup> The complete form was described as including tonic pupil convergence reaction in a pupil unreactive to light and absence or reduction of one or more of the deep tendon reflexes in the lower limbs.<sup>17,19</sup> Incomplete form was described as having tonic pupil only, atypical phases of tonic pupil only, atypical phases of the tonic pupil with absence of tendon reflexes or absence of tendon reflexes only.<sup>17,19</sup>

## The tonic pupil

Adie described the tonic pupil as one that is usually unilateral, with delayed or slow responsiveness to accommodation and convergence.<sup>17</sup> Although there may exist some initial slow responsiveness to light stimulus, the pupil would eventually return to its dilated state after a short delay.<sup>17</sup> A more interesting finding occurs with near-object convergence where the abnormal pupil constricts with increasing slowness to a smaller size than fellow normal eye.<sup>17</sup> Upon

reversal of the convergence effort, the abnormal pupil may either continually contract, remain fixed for a few seconds or begin to dilate at an even slower rate than earlier constriction.<sup>17</sup> The pupil may take as long as several minutes to return to its original size.<sup>17</sup> Accommodation may be affected in a similar manner where the defect mostly occurs during relaxation as vision shifts from near object to distant object.<sup>17</sup> Adie found some variety of the abnormal pupils in terms of shape and size.<sup>17</sup> The size was found to vary during the day, where the pupil was at its smallest in the morning and after crying most likely due to tonic lid-closing reaction.<sup>17</sup> This tonic pupil was also found to react promptly and appropriately to both atropine and physostigmine.<sup>17</sup> Symptomatically, Adie pupil presented with occasional photophobia and blurring of vision if accommodation was involved.<sup>15</sup>

## Comparison to other pupillary disorders

Adie pupil has often been confused with the Argyll Robertson pupil usually seen in syphilis.<sup>17</sup> Clinically, the two can be distinguished.<sup>17</sup> The dilated Adie pupil is always larger than the normal fellow eye, whereas the unilateral Argyll Robertson pupil is always smaller than normal fellow eye.<sup>17</sup> Argyll Robertson pupils are usually miotic, bilateral and fixed to light stimulation but react promptly to convergence.<sup>17</sup> Adie pupil is usually mydriatic, unilateral and contracts slowly in convergence and dilates even slower.<sup>17</sup> Eighty per cent of Adie pupil cases are unilateral, whereas more than 95% of Argyll Robertson pupil cases occur bilaterally.<sup>15</sup> Adie pupil dilates normally to atropine, whereas Argyll Robertson pupil dilates poorly. Argyll Robertson pupil is a feature of syphilis – there is usually significant history and serologic evidence of syphilis.<sup>15</sup> Adie pupil should also be differentiated from other pupillary defects such as internal ophthalmoplegia and iridoplegia of obscure origin.<sup>15</sup>

## Loss or absence of tendon reflexes

In Adie syndrome, the most frequently affected reflex was the loss of one or both Achilles reflexes.<sup>17</sup> Other reflexes such as patellar and bicep reflexes were found to be sluggish. These losses may be asymmetric in nature.<sup>15</sup> Some cases showed loss of both Achilles and patellar reflexes, and even fewer showed involvement of all reflexes.<sup>20</sup>

## Other features

Adie established an increased incidence of the syndrome in women than men.<sup>17</sup> He reported a total of 45 female cases compared with 18 male cases.<sup>17</sup> He

was unable to delineate an age range where this syndrome was commonest in.<sup>17</sup> He also did not elucidate any noteworthy elements in the patients' familial history.<sup>17</sup> The general health of Adie's patients was also unremarkable.<sup>17</sup>

### Association of Adie syndrome to syphilis

With regards to Adie syndrome and syphilis, Adie argued in his essay that 'the tonic convergence reaction in pupils only apparently inactive to light is, in all probability, never a manifestation of syphilis of the nervous system.<sup>17</sup> The combination of this sign with absent tendon reflexes and without other signs of organic nervous disease has never been observed in syphilis of the nervous system; it is not one of its manifestations'.<sup>17</sup>

### Aetiology and pathophysiology

The pathophysiology of Adie syndrome was elucidated in HG Scheie's use of mechoyl test.<sup>15</sup> This study suggested that the tonic pupil is due to a denervation or lesion in the parasympathetic ciliary ganglion or the post-ganglionic ciliary nerves.<sup>15</sup> Histology showing degeneration of nerve cells in ciliary ganglion at site of lesion has been highly suggestive of this.<sup>21</sup> Post-ganglionic axonal regrowth occurs few weeks after the development of lesion at the ciliary ganglion.<sup>21</sup> This leads to axonal synapsis with inappropriate musculature resulting in a diminished response to light and an amplified, tonic reaction to accommodation.<sup>21</sup> This process occurs in a segmental distribution of the affected eye's iris.<sup>21</sup> The denervation of ciliary body generates more postsynaptic acetylcholine receptors. This results in the affected eye becoming highly sensitive to pilocarpine 0.1%.<sup>21</sup> With the administration of the latter, a more exaggerated response occurs in the affected eye than in the normal fellow eye. This method is now used as a useful tool to diagnose Adie's pupil.<sup>21</sup>

The postulated mechanism of areflexia is due to a synaptic disorder of the spinal reflex pathways.<sup>22</sup> Although these new findings add to the clinical portrait of Adie syndrome, its aetiology remains unclear to this day.<sup>23</sup>

The association of this syndrome with other disorders has been suggested for the following: influenza, polyneuritis, encephalitis, multiple sclerosis, orthostatic hypotension, vitamin deficiencies and endocrine disorders, particularly hypothyroidism.<sup>20</sup> Most patients frequently presented with symptoms of nervousness and emotional disorders with palpitations, sweating, anxiety and fear.<sup>20</sup> A series of cases by Kennedy *et al.* provided evidence of instability of the autonomic nervous system associated with emotional disturbances in patients with Adie's syndrome.<sup>24</sup>

### Diagnosis

In his second paper, Adie regarded the tonic pupil with absence of one or more of the tendon reflexes as pathognomonic feature of the syndrome.<sup>17,19</sup> The diagnostic criterion of the tonic pupil includes not only the delay in pupillary movement, but also the slowness of it.<sup>17,19</sup> He raised the importance of distinguishing the syndrome from pupillary involvements seen in retinal disease, iridoplegia and internal ophthalmoplegia.<sup>17</sup> Argyll Robertson pupil must also be carefully distinguished especially to rule out a diagnosis of syphilis – it should be excluded after performing complete studies.<sup>15</sup> Diphtheria was also found to produce ocular symptoms and loss of tendon reflexes, however, the differences in internal ophthalmoplegia aid in exclusion.<sup>15,19</sup>

### Management

Adie's syndrome requires no therapy as it is a benign disorder. Patients may require psychotherapy to address any psychiatric issues. Low dose pilocarpine may be used as both a diagnostic and therapeutic measure.<sup>15</sup>

### Modern context and significance

In the modern ophthalmic context, although the disease definition remains similar, a plethora of new findings have been made with regards to the syndrome.<sup>23</sup> The epidemiology of the syndrome has been uncovered where the incidence was found to be 4.7:100 000 and prevalence to be 2:1000.<sup>23</sup> It was found to affect the younger population with the mean age of patients around 32.2 years.<sup>23</sup> Females were affected 2.6 times more than males.<sup>23</sup> It was also found that the distribution of paralysis to light was random around the sphincter.<sup>23</sup> For treatment purposes, pilocarpine was found to be an effective agent. It was also found that Adie syndrome had the capacity to become worse with time with increased risk of other eye involvement, more complete sphincter paralysis and worsening of deep tendon reflexes.<sup>23</sup>

Since Adie's description of the pupil, it has been reported as an association with various rheumatological disorders, such as Sjögren's disease, temporal arteritis and rheumatoid arthritis.<sup>25</sup> It may also occur as a paraneoplastic syndrome especially with lung and breast malignancies.<sup>25</sup> Additionally, it is associated with peripheral neuropathies involved in amyloidosis, alcohol intake and diabetes.<sup>26</sup> Recent studies have also found a link to chronic cough,<sup>27</sup> autoimmune hepatitis and coeliac disease,<sup>28</sup> and endometriosis<sup>29</sup> where there is a common underlying autoimmune process. However, most occurrences of Adie pupil are spontaneous and idiopathic.<sup>25</sup>

Ross syndrome is a disorder that may be related to Adie syndrome. It is a rare disorder with only 40 cases reported between 1958 and 2006. It is characterized by tonic pupil, reduced or absent reflexes, and segmental anhidrosis likely due to postganglionic autonomic dysfunction in the cranial nerves.<sup>30</sup> A recent study by Nolano *et al.*<sup>31</sup> suggested that Ross syndrome is clinically and pathologically distinguishable from Adie syndrome. However, the relationship between the two remains unknown. Adie syndrome has been proposed as a milder or earlier form of Ross syndrome.<sup>25</sup>

Although Adie syndrome has been associated with a number of reported comorbidities in the literature, it remains a benign disorder.<sup>20</sup> The importance lies in differentiating its complex of symptoms from that of syphilis mainly by distinguishing Adie pupil from Argyll Robertson pupil.<sup>20</sup>

### OTHER SCIENTIFIC WORKS

During his clinically active years (1911–1935), William John Adie's contribution to science was vast. His frequency and scale of writing often did not reflect the substantial clinical experience he possessed. With his colleague, James Collier, he wrote the section on diseases of the nervous system in Price's textbook of Practical Medicine which is considered to be one of the best general textbooks on neurology.<sup>5</sup> He made significant contributions in *Brain* and other scientific journals.<sup>17,19</sup> Some of his most notable work was on myotonic dystrophy,<sup>1</sup> narcolepsy,<sup>1</sup> somnolepsy<sup>1</sup> and pyknolepsy.<sup>1</sup> When he joined the staff of Moorfields Eye Hospital, he became interested in the neurological side of ophthalmology (i.e. neuro-ophthalmology). He wrote about pseudo-Argyll Robertson pupil, pituitary tumours and the ophthalmic aspects of disseminated sclerosis.<sup>3</sup>

Throughout his career, Adie consistently contributed to the scientific community through his numerous case reports. During the 1920s and 1930s, he published a number of them on the following disorders: congenital amyotonia;<sup>32</sup> progressive familial cerebral degeneration;<sup>33</sup> progressive muscular atrophy;<sup>34</sup> disseminated sclerosis;<sup>35</sup> myotonic dystrophy;<sup>36</sup> familial periodic paralysis;<sup>37</sup> hepatolenticular degeneration;<sup>38</sup> and myasthenia gravis.<sup>39</sup>

In 1926, Adie also published a large case series of narcolepsy in association with cataplexy in a clinical essay in *Brain*.<sup>40</sup> He described narcolepsy as 'attacks of irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly so that the victim sinks to the ground fully conscious but unable to move'.<sup>40</sup> His definition is still in line with the modern understanding of narcolepsy and has been cited on many occasions in the medical literature.

### CONCLUSION

As described by one of his students, Adie was an extremely approachable consultant who was never too conscious about his status as a physician. He was seen as someone who inspired a feeling of compassion, resilience and confidence among his colleagues. His relationship with his students was considered to be very personable and interactive – he always saw them as colleagues rather than as juniors. His clinical teaching was unrivalled as he possessed the sought-after ability to express everything in clear and simple language. These qualities would often see him invited as a speaker at various events and medical societies. His clinical lectures were always well attended and described as short, yet comprehensive.<sup>2</sup>

The career of William John Adie may have only spanned just over two decades, but his contributions to medicine were perennial. His extensive work on the description of Adie syndrome led to the formation of a detailed neurologic and ophthalmic understanding. The recognition of the syndrome and its benign pupil provided a needed distinction from the malignant pupil of syphilis. Adie's additional contributions to narcolepsy and his numerous case descriptions serve as the basis of modern understanding of many neurological syndromes. His work has and will continue to play a significant role in the neurologic and ophthalmic arenas.

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### REFERENCES

1. William John Adie, M.D.Ed., F.R.C.P. *Br Med J* 1935; **1**: 624–5.
2. The Late Dr. W. J. Adie. *Br Med J* 1935; **1**: 681.
3. William John Adie, M.D. Edin., F.R.C.P. Lond. *Lancet* 1935; **225**: 717.
4. Obituary of William John Adie, M.D., F.R.C.P. *The Charing Cross Hospital Gazette* 1935; **74**–6.
5. Pearce JMS. William John Adie (1886–1935). *J Neurol Neurosurg Psychiatry* 2004; **75**: 1111.
6. Archive materials from the Queen Square Archives and Museum.
7. Firkin BG, Whitworth JA. *Dictionary of Medical Eponyms: Adie Pupil*. Boca Raton, FL: CRC Press, 2001.
8. Adie WJ. Argyll Robertson pupils true and false. *Br Med J* 1931; **2**: 136–8.

9. Lowenstein O, Lowenfeld IE. Pupillotonic Pseudotabes. *Surv Ophthalmol* 1965; **10**: 129–85.
10. Pearce JMS. Hughlings Jackson and the Holmes-Adie tonic pupil. *J Neurol Neurosurg Psychiatry* 1995; **58**: 87.
11. Ware J. Observations relative to the near and distant sight of different persons. *Philos Tr Roy Soc London* 1813; **103**: 31–50.
12. Jackson H. Paralytic affections: on eye symptoms in locomotor ataxy. *Trans Ophthal Soc UK* 1881; **1**: 139–54.
13. Saenger A. Myotonic pupil movement. *Neurol Centralbl* 1902; **21**: 837–9.
14. Strasburger J. Sluggishness of the pupil to accommodation and convergence. *Neurol Centralbl* 1902; **21**: 738–40.
15. Scheie HG. Site of disturbance in Adie's syndrome. *Arch Ophthalmol* 1940; **24**: 225–37.
16. Markus C. Notes on peculiar pupil phenomena in cases of partial iridoplegia. *T Ophthal Soc UK* 1906; **26**: 50–6.
17. Adie WJ. Tonic pupils and absent tendon reflexes: a benign disorder sui generis; its complete and incomplete forms. *Brain* 1932; **55**: 98–113.
18. Bramwell E. The Holmes-Adie Syndrome; a benign clinical entity which simulates syphilis of the nervous system. *Trans Med Chir Soc Edinb* 1936; 83–92.
19. Adie WJ. Complete and incomplete forms of the benign disorder characterized by tonic pupils and absent tendon reflexes. *Br J Ophthalmol* 1932; **8**: 449–61.
20. Dynes JB. Adie's Syndrome: its recognition and importance. *JAMA* 1942; **119**: 1495–7.
21. Hope-Ross M, Buchanan TAS, Archer DB, Allen JA. Autonomic function in Holmes-Adie Syndrome. *Eye* 1990; **4**: 607–12.
22. Mak W, Cheung RTF. The Holmes-Adie plus syndrome. *J Clin Neurosci* 2000; **7**: 452.
23. Thompson ST. Adie's syndrome: some new observations. *Trans Am Ophthalmol Soc* 1977; **75**: 587–626.
24. Kennedy F, Wortis H, Reichard JD, Fair BB. Adie's syndrome: report of cases. *Arch Ophthalmol* 1938; **19**: 68–80.
25. Moeller JJ, Maxner CE. The dilated pupil: an update. *Curr Neurol Neurosci* 2007; **7**: 417–22.
26. Martinelli P. Holmes-Adie syndrome. *Lancet* 2007; **356**: 1760–1.
27. Ford PA, Barnes PJ, Usmani OS. Chronic cough and Holmes-Adie syndrome. *Lancet* 2007; **369**: 342.
28. Csak T, Folhoffer A, Horvath A *et al.* Holmes-Adie syndrome, autoimmune hepatitis and celiac disease: a case report. *World J Gastroenterol* 2006; **12**: 1485–7.
29. Morelli N, Gallerini S, Cafforio G *et al.* Adie tonic pupil associated to endometriosis. *Neurol Sci* 2006; **27**: 80–1.
30. Hagemann G, Bartke T. Adie's pupil in the Ross syndrome. *N Engl J Med* 2006; **355**: 6.
31. Nolano M, Provitera V, Perretti A *et al.* Ross syndrome: a rare or a misknown disorder of thermoregulation? A skin innervation study on 12 subjects. *Brain* 2006; **129**: 2119–31.
32. Adie WJ. A family affected with amyotonia congenita. *Proc R Soc Med* 1926; **19** (Sect Study Dis Child): 2–3.
33. Adie WJ. A family with progressive familial cerebral (so-called Cerebro-Macular) degeneration. *Proc R Soc Med* 1926; **19** (Sect Study Dis Child): 1–2.
34. Adie WJ. Case of progressive muscular atrophy occurring forty-two years after infantile paralysis. *Proc R Soc Med* 1924; **17** (Neurol Sect): 58.
35. Adie WJ. Observations on the aetiology and symptomatology of Disseminated Sclerosis. *Br Med J* 1932; **2**: 997–1000.
36. Adie WJ. Case of dystrophia myotonica. *Proc R Soc Med* 1923; **16** (Neurol Sect): 45.
37. Adie WJ. A case of familial periodic paralysis. *Proc R Soc Med* 1927; **20**: 1837.
38. Adie WJ. Hepato-lenticular degeneration. *Proc R Soc Med* 1929; **23**: 90.
39. Adie WJ. Myasthenia gravis in a boy aged 10. *Proc R Soc Med* 1927; **20**: 1838.
40. Adie WJ. Idiopathic narcolepsy: a disease sui generis: with remarks on the mechanism of sleep. *Brain* 1926; **49**: 257–306.