# Alice in Wonderland syndrome throughout history: a narrative view through the eyes of Lewis Carroll

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#### **ABSTRACT**

**Introduction.** Alice in Wonderland syndrome is a clinical picture, appearing in Lewis Carroll's work of the same name, characterised by brief episodes of distorted perception; it has been associated with different entities over the years.

**Objective.** To analyse the growing understanding of migraine, from the historical perspective of Lewis Carroll's experience, with special emphasis on Alice in Wonderland syndrome.

**Methods.** A literature search on PubMed and critical review of the literature were used as the basis for a historical narrative.

**Results.** With Lewis Carroll as the protagonist, the narrative analyses the most representative thought on Alice in Wonderland syndrome and migraine, drawing on the available information on the aetiology, pathophysiology, and treatment of the syndrome throughout history, represented as stories concealed behind doors and mirrors.

**Discussion.** This scientific-literary text demonstrates the relevance and growing understanding of Alice in Wonderland syndrome, contributing information on its pathophysiology (possible parieto-occipital dysfunction, predominantly in the right hemisphere) and aetiopathogenesis (migraine, epilepsy, and certain infections), as well as its treatment according to the underlying cause, through a historical narrative following Lewis Carroll, a key figure in the dissemination of this phenomenon.

#### **KEYWORDS**

Migraine, aura, Alice in Wonderland syndrome, headache, Lewis Carroll

#### Introduction

One morning in 1874, an ill-tempered Charles Lutwidge Dodgson was taking his breakfast when he found a promising note in the newspaper: "Another [remedy] for pains in one side of the head: skull of silirus-fish is boiled with oil, and the head is rubbed therewith for four days," a remedy mentioned in the Ebers Papyrus (ca. 1500 BC), shown in Figure 1.

<sup>A</sup>Translator's note: English translation taken from Ebbel B. The Papyrus Ebers. London: Oxford University Press; 1937.

Thus, nearly 3500 years before, the honour of curing migraine appears to have belonged to a freshwater fish, according to that old medical treatise and pharmacopoeia discovered by the German Egyptologist Georg Ebers.<sup>1</sup>

"I fear that even the Egyptians were unable to free themselves from this torture," muttered Charles, or rather Lewis, whom Charles had become after the publication of *Alice in Wonderland*...

Charles Lutwidge Dodgson (an Anglican deacon, logician, mathematician, photographer, and writer) had until then been the real name of Lewis Carroll, author of

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**Figure 1.** Ebers Papyrus. Modified from: Rodríguez-Badiola MI. Apuntes sobre el papiro Ebers. *Boletín de la Asociación Española de Egiptología*. 1997;7:43-56.

Alice's adventures in Wonderland and Through the looking-glass, and what Alice found there.

Born on 7 January 1832 in the United Kingdom, Lewis died at the age of 66 years; but now, he was trying to do away with that terrible headache that so often tormented him, casting a dark cloud over his ordinarily cheery demeanour.

Unhappily, Lewis was becoming accustomed to those unpleasant moments provoked by pain; sometimes (Figure 2), he noticed changes in the shape (metamorphopsia), size (macropsia, micropsia), and position (teleopsia, "dolly zoom" effect) of objects, and even distortions of body image (macro- and microsomatognosia). Other times he perceived illusory alterations in the passage of time, and later (after 30 to 40 minutes) he would experience intense pain, beginning on one side of the head and occasionally spreading to the other, incapacitating him.<sup>2</sup> Would this pain be a constant for the rest of his life?

"I shall have to consult a specialist," he thought, and in the words of the March Hare, "it's getting late..."

Like his creation Alice, one afternoon in the woods near his house, Lewis undertook an unexpected journey down a rabbit hole. At the end of the tunnel, he was met with a series of doors, the same as in his story, but this time with golden plaques above the peepholes, bearing names and dates.

"I shall begin at the beginning," he said to himself, and began snooping around to find out what was hidden behind each of them.

#### Methods

The information behind each of the doors visited by Lewis Carroll is based on a literature search on PubMed

conducted in November 2022, with the search term "Alice in wonderland syndrome." The search yielded 163 results. The historical narrative is based on information extracted from articles selected according to the following criteria: 1) scientific articles and reviews with abstracts available; 2) articles cited in the references sections of the articles used; and 3) articles including information on the pathophysiology, aetiopathogenesis, and/or treatment of entities progressing with so-called Alice in Wonderland syndrome, with a particular focus on migraine. Articles without abstracts or whose full texts could not be retrieved were excluded. Articles reporting similar information were also excluded, prioritising those that address the syndrome from the perspective of migraine. A total of 12 articles were selected that reported recent, updated, and complete information regarding the pathophysiology, aetiopathogenesis, and/ or treatment of Alice in Wonderland syndrome, focusing on its relationship with headache. Some articles not indexed on PubMed were also consulted, either due to their inclusion in the references sections of the scientific articles or due to their relevance to the historical narrative.

#### Results

During his journey, Lewis Carroll discovered that behind the different doors, representing different historical moments, were the most representative ideas in the context of each period on migraine and Alice in Wonderland syndrome (Figure 3).

The first door: Hippocrates, 460 BC. Shortly after entering the door, and after greeting the Greek father of medicine, Lewis could not resist asking the great physician's opinion on his ailment. Without a doubt, Hippocrates'

explanation was a curious one: "pain is caused by the accumulation in the head of vapours from the stomach; it can be partially alleviated by vomiting."<sup>3</sup>

The recommendation to alleviate headache by inducing vomiting was rather excessive and, today, ill advised, although it is less invasive than the trepanation performed in the neolithic age to release the demons that caused pain.<sup>4</sup>

"Let's try the second door, and see what we find," thought Lewis: Galen, 129 AD. In the second century AD, the great Greek physician Galen also described the disease that so bothered Lewis. He also contributed pathophysiological theories, postulating that migraine was explained by irritation of intracranial structures by yellow bile, and that the characteristic pulsatile pain was provoked by blood vessels in contact with the falx cerebri, explaining the involvement of one half of the brain and the meninges. The concept of pain affecting half of the head (hemicrania) is the origin of the terms "migraine" in English and "migraña" in Spanish.<sup>5,6</sup>

"What a useful fact: there can be no doubt! Words give us clues about their meaning." Indeed, in half of his head he felt the pulses that had him writhing in pain as he led in the dark waiting for the episode to end: half a being causing disability of the whole. Migraine?

At the next door, Lewis Carroll discovered another name and another date: Avicenna, 980 AD. He needed no key, nor to grow or to shrink: he gave the slightest knock with the knuckles of his right hand, and the door swung open.

"How may I help you?" asked Avicenna.

This time, a different word was used to refer to the pain: "*jaqueca*" (which in Arabic means "half," but describes the same sensation, the same pain, the same half, the same ailment).<sup>7</sup>

Avicenna recommended that Lewis read his work *The canon of medicine*, which included various herbal remedies for *jaqueca*, including opium (a drug that he not only prescribed to all of his patients, but which also led to his untimely death due to intoxication caused by his disordered consumption of the substance).<sup>8</sup>

As an aside, different medications were available in 1874 for the treatment of migraine with or without aura, but there had also historically been alternative treatments with nutraceuticals or dietary/herbal supplements like those proposed by Avicenna: riboflavin (vitamin B<sub>12</sub>), for

example, had previously been suggested as a preventive treatment for migraine; other suggestions included milk, green vegetables, and rice in sufficient amounts; and increased intake of nuts (rich in magnesium, another compound that later came to be widely used for migraine prevention), fish and liver (rich in coenzyme Q10), eggs (melatonin), linseed (thioctic acid), tuna or mackerel (vitamin D), and legumes (vitamin B<sub>3</sub>). In other words, migraine could be prevented with a rich, varied diet. 9,10

But, what could be done if this approach was ineffective? Another possibility was phytomedicine, the use of plants containing medicinal substances: Damask rose, chamomile, ginkgo, and lavender oil had traditionally been used as topical treatments to reduce pain, and clinical trials have even sought to establish the level of evidence for their use.<sup>11</sup>

In short, different paths were available for the treatment of migraine. And they were all welcome!

To continue our journey with Lewis, let us visit the next door: Abbess Hildegard von Bingen, 1098.

The visitor was overwhelmed by her astonishing blue eyes. Small, slim, and very clever, the Sybil of the Rhine, as she was known, decorated her walls with prints that were very familiar to Lewis, showing a mystical, ineffable interpretation of migraine with aura, a condition that she had suffered since childhood. Lewis' protagonist Alice almost could have run through the open fields of Hildegard's codices *Scivias* and *Liber divinorum operum.*<sup>12</sup> As an aside, in one one of her studies Hildegard emphasised the pain relief offered by cannabis in migraine, recognising the properties that are currently under study in this field, and are widely used in such other paroxysmal diseases as epilepsy.<sup>13</sup>

The next door featured a semicircular arch, flanked on each side by a column topped by a classical capital, announcing the name of the physician who stood behind it: Paracelsus, 1540.

The Renaissance brought about a radical change in conceptions of the world and of humanity; Paracelsus deduced the anaesthetic value of ether (although it was not used in earnest for another 300 years) and described his seven rules for life: drinking water, banishing negative ideas, doing good, forgetting offences, meditating, being prudent with personal affairs, and feeling no fear about the future. Paracelsus dared to criticise some of the classical masters of medicine: on Galen and Avicenna, he







**Figure 2.** Illustrations of manifestations of Alice in Wonderland syndrome. A) Metamorphopsia. B) Microsomatognosia. C) Macrosomatognosia. Illustrations by Sir John Tenniel (1820-1914).

said that "there is more wisdom in the laces of my shoes than in these old men"; "all the universities, and all the old writers put together are less gifted than the hairs of my beard." <sup>14</sup> He combined astronomy and alchemy, and it is known today that health depends to an extent on diet and such "salutary" supplements as riboflavin, magnesium, and coenzyme Q10, which are probably efficacious in migraine prophylaxis. <sup>15</sup>

It was simply a question of proving it; for too many centuries had people suffered. Babylonian documents dating from 3000 BC described situations that may correspond to migraine with aura, and Sumerian texts from the same period also addressed the disease. <sup>16</sup>

Even the gods could not free themselves of this damnation: Greek literature recounts how Zeus suffered severe headaches; Hephaestus tried to alleviate the pain by splitting open his head with an axe, causing the birth of Athena, the goddess of wisdom.<sup>17</sup>

However, this monster of half the head remained undefeated, and continued tormenting people. Had the golden age really been unable to find a solution? Evidently, it

had. Another two centuries would pass before a moderately effective treatment would be developed.

Above the next door was an English name: Thomas Willis, 1621.

"Come along, dear Lewis, I should be delighted to talk with you!," said Willis.

The two had a polite conversation, but the much desired solution to the problem did not materialise; however, the eminent pioneer of neurology ventured that the pain may be of vascular origin. This was the oldest and best supported theory, although it did not account for all the pathophysiological phenomena underlying the disease. 18,19

Lewis continued advancing through the labyrinth of doors, but the elusive remedy had not yet appeared; he was tempted to abandon his search, when he glimpsed another door: Robert Whytt, 1714.

Whytt, who had originated the concept of "nervous disease," proposed another approach: migraines associated with hysterical convulsions, vertigo, double vision, and clouded thought as a result of confusion.<sup>20</sup> However,

Lewis was not wholly convinced by this interpretation of his migraine and, probably, of the visual alterations he experienced.

Thus, though the approach was different, he still lacked any specific treatment, and decided to go on his way, leaving behind the remaining doors and searching for the way out of the rabbit hole.

If he later decided to return to that labyrinthine place, he would probably find another interesting door, that of Charles Singer, 1876.

And he would notice how the previous observations and references were beginning to make sense, for Charles Singer identified the men of science who had described migraine and performed an excellent review of the most characteristic phenomena in this disease,<sup>21</sup> although it was not yet known by its current name.

In fact, it was Caro W. Lippman, in 1952, who first described the syndrome that tormented Lewis, and John Todd, in 1955, who named it Alice in Wonderland syndrome, in honour of the writer: Lewis Carroll had suffered with migraines, and had probably projected onto his creation the manifestations that he experienced during attacks. This is the only way we may interpret Todd's assertion that "Alice trod the paths and byways of a Wonderland well known to her creator." <sup>22,23</sup>

Lippman and Todd were further supported by Oliver Sacks' work *Hallucinations*. Should Lewis Carroll have met Sacks on his journey through that terrible passageway, he would have heard words similar to the following:

"Welcome, Mr Carroll! Please, won't you join me, so we may talk about your *Alice* and our syndrome?" Indeed, among the 24 strange cases recounted by Oliver Sacks in his book *The man who mistook his wife for a hat* is a case of micropsia, which he later described as "Alice in Wonderland syndrome" in *Hallucinations*.

Lewis would also see, after opening Sacks' door, that there was a hope of controlling the syndrome. And he would be very grateful to the fictional beings who enabled him to live before, and beyond, his biological life. He was finally beginning to unravel the mystery: there would be different causes, scientific studies, and potentially effective treatments. Science promised that the story would become reality.

In the 21st century, the question was further elucidated. If Lewis had opened that door, he would have jumped

for joy: from that time, Alice in Wonderland syndrome, or dysmetropsia, would be defined as a clinical picture characterised by brief episodes of perceptual changes related to body image, size, distance, or spatial relations, in association, just as he had suspected, with migraine, infection, epilepsy, or mononucleosis.

And Lewis would have begun to hear of other cases reported in the medical literature. Further down the rabbit hole, he would advance through the hall of doors inside, glimpsing a light and a way out at the end. He would continue to the surface, finding no forest, no Queen of Hearts, no Cheshire Cat, and no Mock Turtle; instead, he would find a series of mirrors, each reflecting a figure.

In the first was an old man worrying about his son. The 74-year-old, with history of migraine without aura, had seen his son's arm grow increasingly large. A magnetic resonance imaging study revealed a haemorrhage in the right occipital lobe; alongside complementary studies, this confirmed the diagnosis of cerebral amyloid angiopathy. The visual hallucinations resolved after treatment with antiepileptic drugs.<sup>26</sup>

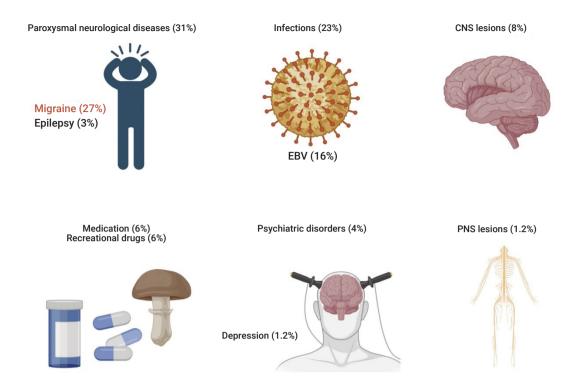
Further along the corridor, in the second mirror, was an old woman, in tremendous sorrow. This woman, 95 years old, without history of cognitive impairment, attended the emergency department due to concerns after seeing people with very small hands. She reported that images were distorted, and that her family members' heads appeared very large if they approached her from the left; she also saw animals coming from the same side. A head CT scan revealed ischaemic stroke in the territory of the right posterior cerebral artery.<sup>27</sup>

Another mirror showed an adolescent girl with a sad face. The 15-year-old brunette reported that her head and hands were enormous and that she could not drink water because the glass was too close or too far from her mouth. Other members of her family were also affected, and episodes occurred several times per day. In this case, hallucinations were caused by Zika virus.<sup>25</sup>

Finally, as though tracing a lifetime in reverse, the last mirror showed a young child. The 11-year-old reported that she experienced up to four episodes per day, lasting two or three minutes each, in which her hands appeared large and her pen small. The child was taking montelukast; in the absence of any other suspected trigger factor, the treatment was suspended and her condition improved, with symptoms disappearing.<sup>28</sup>



**Figure 3.** The main physicians and other figures involved in the management of migraine and Alice in Wonderland syndrome throughout history. A) Hippocrates (460-370 BC). B) Galen (129-216 AD). C) Avicenna (980-1037). D) Abbess Hildegard von Bingen (1098-1179). E) Paracelsus (1493-1541). F) Thomas Willis (1621-1675). G) Robert Whytt (1714-1766). H) Lewis Carroll in 1865. I) Charles Singer (1876-1960). J) Caro W. Lippman in 1952. K) John Todd in 1955. L) Oliver Sacks in 2013.



**Figure 4.** Main aetiologies of Alice in Wonderland syndrome. CNS: central nervous system; EBV: Epstein-Barr virus; PNS: peripheral nervous system. Created with Biorender. Based on data reported by Blom et al.<sup>29</sup> (2016).

Lewis Carroll would find more and more mirrors, in which he would recognise all these symptoms: micro- or macrosomatognosia (sensation of the body being large or small compared to the environment), aschematia (some parts of the body ceasing to be part of the sense of the body) or metamorphopsia (disorders of visual perception), palinopsia (recurrent perception after disappearance of the original visual stimulus), prosopagnosia (inability to recognise familiar faces), teleopsia (objects appearing more distant than they are), peleopsia (objects appearing closer than they are), achromatopsia (loss of colour vision), polyopia (subject receiving several visual images of a single object), and akinetopsia (inability to perceive the movement of objects).<sup>28</sup>

The author of *Alice in Wonderland* would continue through that forest, animated by the reflections of pa-

tients with these symptoms, and think about how useful a statistical analysis would be: such a study would reveal that the entity most frequently associated with the syndrome is migraine (27.1%), followed by infections (22.9%), brain lesions (7.8%), use of medications (6%) or recreational drugs (6%), psychiatric disorders (3%), and peripheral nervous system disorders (1.2%), among many others.<sup>29</sup> However, the cause is not established in up to 20% of patients.<sup>30-32</sup> The most representative groups of diseases and aetiologies in each group are shown in Figure 4.

Such would be the story of this disease, which mainly affects children, but also adults.<sup>33</sup> A prevalent syndrome in patients with migraine, and especially in those experiencing aura, which tends to occur at a similar time to pain attacks, suggesting the existence of shared patho-

physiological mechanisms.<sup>3</sup> It has been suggested that the syndrome may be related to parieto-occipital dysfunction that preferentially, but not exclusively, affects the right hemisphere.<sup>34-36</sup>

Thus, little by little, Lewis Carroll would see that he was coming increasingly close to understanding and controlling his disease. Researchers were identifying ever more causes and more treatments for the underlying pathology. For instance, appropriate doses of calcium channel blockers, beta blockers, or topiramate,<sup>29,37</sup> and even transcranial magnetic stimulation<sup>38</sup> (basically, preventive treatments for migraine) reduced the risk of developing this syndrome,<sup>34</sup> feeding new hopes for Lewis.

#### Conclusion

The data gathered on the history of migraine and Alice in Wonderland syndrome, a prevalent complication, sheds light on various aspects of the disease: its pathophysiology, with the presence of parieto-occipital dysfunction, predominantly in the right hemisphere, thought to play a role; its aetiopathogenesis, with the syndrome appearing in patients with such paroxysmal neurological diseases as migraine or epilepsy, as well as some infections; and its treatment according to the underlying cause.

To return to the narrative of Lewis Carroll: with all the information found behind the different doors and mirrors, there appears to be no need to apply the expedited, categorical remedy of the Queen of Hearts: "Off with their heads!"

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#### Conflicts of interest

Alicia Gonzalez-Martinez has received lecture honoraria from TEVA.

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