

## A NARRATIVE REVIEW BASED ON CAUSES AND CONSEQUENCES OF THE ALICE IN WONDERLAND SYNDROME

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### ABSTRACT

**INTRODUCTION:** The Alice in Wonderland Syndrome (AIWS) is a rare clinical neurological condition, based on the presence of perception disorders which are interpreted by the patient as rare metamorphosing and depersonalization events. The main goal of this research is to analyze the causes and consequences of the Alice in Wonderland Syndrome. **METHODOLOGY:** In the process of creating this narrative review, the BVS, Scielo and PUBMED databases were consulted. The following filters and inclusion criteria were used: English, Portuguese, Spanish AND last 5 years. **RESULTS:** The most common causes of AIWS are infections by the Epstein-Barr virus and migraines. Symptoms include visual illusions in which the patient sees altered object dimensions, changes in the shape (metamorphopsia) and even notice the disappearance of objects (palinopsia) and the appearance of animals (zoopsy). **DISCUSSION:** The analysis of the articles showed that the main cause of AIWS is infection by Epstein Barr virus. There were reports including other causes, such as: epilepsy, migraines, infections by other viruses, consequences of surgery and drugs and medications. The majority of patients include young people and children with female predominance. The physiopathology of this disease is not fully understood, but some studies believe that there's the involvement of the occipital, temporal, and parietal lobes. **CONCLUSION:** AIWS remains a poorly known and misdiagnosed syndrome. This instability in the diagnostic process is because no univocally accepted diagnostic criteria for this disease has been developed. Further studies must be performed to achieve better comprehension of the syndrome.

**KEYWORDS:** *Consequence Analysis; Root Cause Analysis; Alice in Wonderland Syndrome.*

### INTRODUCTION

Alice in Wonderland Syndrome is a disorienting perceptual disorder characterized by discrete episodes of bizarre visual illusions and spatial distortions which has been associated with numerous neurologic and psychiatric conditions<sup>1</sup>.

The Alice in Wonderland Syndrome (AIWS) was coined by John Todd on the "Canadian Medical Association Journal" in 1955, who called it «Alice in Wonderland syndrome», attributing its meaning to a group of symptoms associated with migraines and epileptic episodes as its main symptoms<sup>1</sup>. However, historically, the first mention of the group of AIWS

symptoms was made by Caro Lippman in 1952. Lippman documented that some of his migraine patients had auras similar to Alice's in Lewis Carroll's novel "Alice in Wonderland"<sup>2</sup>.

The idea that Lewis Carroll was a migraineur has been proven by his diaries<sup>3</sup>. He often reported a "bilious headache" with vomiting<sup>4</sup>. In the story of Alice's Adventures in Wonderland by Lewis Carroll, Alice experienced a sensation of being changed into being short or tall physically, and also illusionary changes in size, distance and position of objects.

In the stories made by Lewis Carroll, Alice experienced many strange feelings, such as slowing in time perception, whilst falling down the white rabbit's hole. Another example is that her body shrank after drinking from a bottle labelled "DRINK ME"; then she ate a cake and became so large that she touched the ceiling (figure 1). Those are cases in which Alice experienced partial macrosomatognosia and total macrosomatognosia. As the novel progressed, she experienced a feeling that could be identified as depersonalization:

AIWS can occur at any age but is mostly seen in children and it is not individually related to a single medical condition but can rather have several causes and consequences<sup>5</sup>, which will be the main topic throughout this article. In addition, there will be a discussion to understand the different physiopathology and

etiology of the disease, as well as describing possible outcomes for AIWS patients in their daily life.

This narrative review intends to gather some important information about the syndrome and to bring light to the topic and the importance of more research about its implications on people who have the diagnoses to provide a better quality of life for them.

The main intentions of this research are to group the current knowledge about Alice in Wonderland Syndrome, as a way to elucidate the disease. The specific intentions are to understand its origin, the causes and consequences of AIWS and to interpret its effect on the quality of life of those who have it.

**FIGURE 1. Alice in her adventure through Wonderland.**



*Subtitle: Original figures from Lewis Carroll's book, Alice in Wonderland, showing her size in relation to animals and her own appearance with a long neck, a large head or thin and small arms. Reference: Carroll L. Alice's adventures in Wonderland. New York: MacMillan; 1865.*

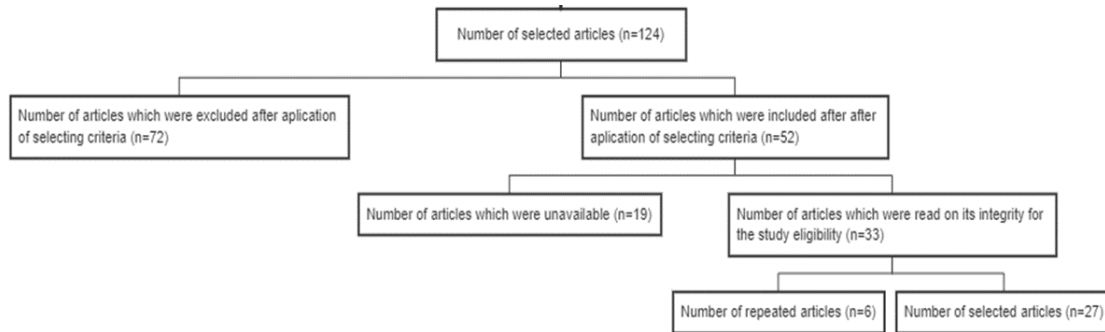
## METODOLOGY

In the process of creating this narrative review, the BVS, Scielo and PUBMED databases were consulted. In the selection of articles, we used the keywords: "Consequence Analysis"; "Root Cause Analysis" and "Alice in Wonderland Syndrome". The following filters and inclusion criteria were used: English, Portuguese, Spanish AND last 5 years. In the BVS database we found 63 articles, of which 55 were eliminated because of the exclusion criteria: repetition, the text was not scientific articles, not focused on causes or consequences or wasn't available. In the PUBMED database we found 55 articles,

among which 17 were excluded due to the exclusion criterias. Finally, in Scielo, 6 articles were found, but all were excluded because they were repeated. Regarding PUBMED, among the 38 articles previously selected, 19 articles were excluded because they did not fit the theme proposal, because they were either letters to the editor or not available for reading. From the total of selected articles, about 27 were included in the research.

Table 1 shows the process of article selection:

**TABLE 1. Process of article selection.**



*Flowchart 1: Process of article selection. In the end, 27 articles were selected. Reference: The authors themselves.*

## RESULTS

This article is a narrative review about “Alice in Wonderland Syndrome”. During the process of researching we found 124 articles. From the total of selected articles, about 28 were included in the research, which were 18 case reports, 6 narrative reviews, 1 original article and 1 systematic review. 1 of them was the book “Alice in Wonderland”.

The analysis of the articles showed that the main causes of AIWS are infections, especially the Epstein-Barr virus<sup>6</sup>, migraines, epilepsy, influenza virus<sup>7</sup>, zika virus<sup>8</sup>, mycoplasma infection<sup>9</sup>, optical neuromyelitis caused by varicella<sup>10</sup>, severe malaria<sup>11</sup>, drugs and medications, such as topiramate and montelukast<sup>12</sup> and transient episodes due to ventriculoatrial shunt<sup>13</sup>. The majority of patients include young people and children with female predominance. The onset of the disease usually occurred before the age of 25<sup>14</sup>.

A study performed gathered 28 patients with migraine or tension-type headaches for 30 years. The results presented were that 78% of patients experienced distortion of objects, 55% reported things seeming much bigger than they were supposed to, 33% saw objects as much smaller than they are, and 55% experienced a feeling that body parts changed in size, all symptoms related to AWS<sup>2</sup>.

Brain computed tomography (CT) and MRI usually show no alterations. The electroencephalogram presented alterations in patients with an etiology of epilepsy. Single-photon emission CT (SPECT) studies were conducted -imaging test that shows how blood flows to tissues and organs- which reveal hypoperfusion of the temporal lobes and around the optic tract and its connections. Studies with SPECT demonstrated that visual evoked potentials showed increased amplitude that could be the driver for transient ischemia localized in the optic tract or of an imbalance in neurotransmitters in the central nervous system.

The cause of this syndrome is still not fully understood yet. However, out of 166 cases of AIWS published, the most common cause is migraine (27.1%), followed by infections (22.9%), principally Epstein-Barr Virus (15.7%). In decreasing order, other etiologies are as follows: brain lesions (7.8%), medicament (6%) and drugs (6%), psychiatric disorders (3.6%), epilepsy (3%), disease of the peripheral nervous system (1.2%), and others (3%)<sup>9</sup>. The drugs associated with the AIWS are LSD and marijuana<sup>15</sup>. In addition, medications, such as Topiramate and dextromethorphan, can lead to this situation<sup>12</sup>.

The symptoms of Alice in Wonderland Syndrome have been attributed to functional and structural aberrations of the perceptual system<sup>16</sup>. The pathophysiology explanation considers that there would be an involvement of the occipital, temporal, and parietal lobes<sup>17</sup>. Occipito-temporal lobes are considered responsible for visual disorders such as phosphenes scotoma, teichopsia, while alterations of the parietal lobe cause the lack of spatial location and appearance of visual perceptions, such as dysmetropsias. Temporo-parietooccipital junction or carrefour region is considered the starting point of AIWS<sup>18</sup>.

A diagnostic criteria for Migraine-related AIWS was proposed in 2015, which can be seen in the table 2 below<sup>6</sup>.

Most of the cases of AWS are reported through childhood and adolescence, and it can still persist through adulthood<sup>4</sup>. The group of symptoms include visual illusions in which the patient suffers metamorphopsia and even notice palinopsia and zoopsy. In relation to the migraines, it could be inherited, especially through the mother<sup>1</sup>. It is worth mentioning that there are no present case studies that associate AIWS with synesthesia<sup>7</sup>.

This syndrome may precede a migraine and be presented as an aura<sup>1</sup>. Occasionally it might be accompanied by depersonalization, when the person feels disconnected or detached from one's body and thoughts and altered perception of time<sup>19</sup>. Other symptoms are presented, such as alterations in hearing and tactile perception, feeling like levitating, demonstrating fear and even terror during the clinic manifestation<sup>1</sup>. In general, with

migraine preventive therapy such as therapy and relaxation training, the resolution of symptoms occurs between one or two weeks, even reaching three months<sup>14</sup>. There are no neurological consequences, besides when the syndrome is related to encephalitis from Epstein-Barr Virus<sup>20</sup>. The episodes may occur several times during the day and last less than 24 hours. In most cases, the presentation is episodic and sometimes it may evolve towards chronicity<sup>19</sup>.

Visual symptoms of AIWS arise several seconds after any visual fixation. This could demonstrate a dysfunction in the parietal-temporal-occipital region<sup>5</sup>, specially an attention-induced augmented activity in the visual association area and in the extrastriate cortex<sup>15</sup>. Recently, functional magnetic resonance imaging presented occipital hypoactivation and parietal hyperactivation in a child with Alice in Wonderland syndrome in comparison to a control participant<sup>21</sup>.

## DISCUSS

The analysis of the articles showed that the main cause of AIWS is infection by Epstein Barr virus. There were reports including other causes, such as: epilepsy, migraines, infections by other viruses, consequences of surgery and drugs and medications. The majority of patients include young people and children with female predominance. The onset of the disease usually occurred before the age of 25<sup>14</sup>. The physiopathology of this disease is not fully understood, but some studies believe that there's the involvement of the occipital, temporal, and parietal lobes. Probably, there's an alteration of an attention-induced augmented activity in the visual association area and in the extrastriate cortex<sup>14</sup>.

The group of symptoms include visual illusions in which the patient suffers metamorphopsia and even notice palinopsia and zoopsy. This syndrome may precede a migraine and be presented as an aura. Some studies show that metamorphopsias may last for seconds or minutes and will be modified after maintaining eyesight on 1 single object; however, during the perception process, objects will most likely not be seen as distorted<sup>22</sup>. This could be explained by cerebral asthenopia, which is the fatigability of the perception system<sup>23</sup>. During the acute phase of AIWS, a patient would not be able to drive or perform fine precision work since this syndrome disrupts one's perception<sup>24</sup>.

Also, physical and mental stress influences the aggravation of migraine headaches<sup>25</sup>. The clinical presence of both depressive episodes and AIWS are commonly seen, in which the frontal cortex hypometabolism is probably related to the depressive symptoms<sup>26</sup>.

Since the symptoms may appear rapidly, the patient must be cautious and prepared, even if they are not experiencing the symptoms yet. This could influence the ability of maintaining a job and interpersonal relationships, since they are limited and socially withdrawn to hide the symptoms. Once AIWS resolves,

a patient should resume their regular activities. The prognosis of AIWS is excellent, since it is a benign self-limiting occurrence<sup>27</sup>.

## CONCLUSION

This analysis showed that the most common causes of AIWS are the infections by the Epstein-Barr virus and migraines. This syndrome usually occurs in children and young people, aged less than 25 years old. Most common symptoms are especially alterations of the perception of their bodies and the space, in which the patient can relate episodes of microsomatognosia and macrosomatognosia. Usually, symptoms last up to two weeks. Currently, there is no treatment and diagnosis criteria for this condition. Further studies must be performed to achieve better comprehension of the AIWS and its effect on the daily life of those who have it.

## CONFLICTS OF INTEREST

There was no conflict of interest.

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## REFERENCES

1. Shah, A.; Maganā, S. M.; E. Youssef, P. Do You See What I See? A Case of Alice in Wonderland Syndrome With EEG Correlate. *Child Neurology Open*, v. 7, p. 1-4, 1 jan. 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7294370/>
2. O'Toole, Patrick ; Modestino, Edward Justin. Alice in Wonderland Syndrome: A real life version of Lewis Carroll's novel. *Brain and Development*, v. 39, n. 6. 2017 p. 470–474. <https://pubmed.ncbi.nlm.nih.gov/28189272/>
3. Carroll L. *Alice's adventures in Wonderland*. New York: MacMillan; 1865.
4. Giulio Mastria; Mancini, Valentina; Alessandro Vigano; et al. Alice in Wonderland Syndrome: A Clinical and Pathophysiological Review. *ResearchGate*. 2016 <https://www.hindawi.com/journals/bmri/2016/8243145/>
5. Rastogi, Reena Gogia; Vanderpluym, Juliana ; Lewis, Kara Stuart. Migrainous Aura, Visual Snow, and "Alice in Wonderland" Syndrome in Childhood. *Seminars in Pediatric Neurology*, v. 23, n. 1. 2016. p. 14–17. <https://pubmed.ncbi.nlm.nih.gov/27017016/>
6. Vara, F. J. M. et al. Síndrome de Alicia en el País de las Maravillas e infección por virus de Epstein-Barr. *Pediatr. aten. prim*, v. 21, n. 1139-7632, p. e67–e70, 2019. <https://pesquisa.bvsalud.org/porta/resource/pt/ibc-184588>
7. Kubota, Kazuo; Shikano, Hiroaki; Fujii, Hidehiko; et al. Alice in Wonderland syndrome associated with influenza

- virus infection. *Pediatrics International*, v. 62, n. 12. 2020. p. 1391–1393. <https://pubmed.ncbi.nlm.nih.gov/33145932/>
8. Paniz-Mondolfi, Alberto E.; GIRALDO, José; Rodrigues-Morales, Alfonso J.; et al. Alice in Wonderland syndrome: a novel neurological presentation of Zika virus infection. *Journal of NeuroVirology*, v. 24, n. 5. 2018. p. 660–663. <https://pubmed.ncbi.nlm.nih.gov/30105501/>
  9. Omata, T. et al. Alice in Wonderland syndrome associated with mycoplasma infection. *Pediatrics International*, v. 58, n. 10, p. 1057–1059, 31 ago. 2016. <https://pubmed.ncbi.nlm.nih.gov/27577175/>
  10. Trevizol, A. P. et al. Alice in Wonderland syndrome secondary to optical neuromyelitis caused by varicella. *The Australian and New Zealand Journal of Psychiatry*, v. 52, n. 8, p. 805–806, 1 ago. 2018. <https://pubmed.ncbi.nlm.nih.gov/29716388/>
  11. Kadia, B. M.; Ekabe, C. J.; Agborndip, E. Primary care challenges of an obscure case of “Alice in Wonderland” syndrome in a patient with severe malaria in a resource-constrained setting: a case report. *BMC Infectious Diseases*, v. 17, n. 1, p. 1–4, 1 dez. 2017. <https://pubmed.ncbi.nlm.nih.gov/29272995/>
  12. Fonseca, R. S. S. et al. Síndrome de Alicia en el país de las maravillas secundario a consumo de montelukast. Presentación de caso. *Revista Médica Electrónica*, v. 43, n. 2, p. 3222–3230, 1 abr. 2021. <https://www.google.com/url?q=https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1251939&sa=D&source=editors&ust=1629675579876000&usg=AOvVaw2iOrkwuZIW1oYOLn1GZf1E>
  13. Entezami, P. et al. Transient Episode of Alice in Wonderland Syndrome After Ventriculoatrial Shunt Revision. *World Neurosurgery*, v. 121, n. , p. 149–151, jan. 2019. <https://pubmed.ncbi.nlm.nih.gov/30326315/>
  14. Chirchiglia, D.; Chirchiglia, P.; Marotta, R. A singular association of migraine with brainstem aura and Alice in Wonderland syndrome. *Child’s Nervous System*, v. 35, n. 8, p. 1435–1437, 2 maio 2019. <https://pubmed.ncbi.nlm.nih.gov/31049666/>
  15. Mastria, G. et al. Temporal–occipital glioblastoma presenting with Alice in Wonderland Syndrome in a patient with a long-time history of migraine without aura. *Neurocase*, v. 24, n. 5-6, p. 242–244, 2 nov. 2018. <https://pubmed.ncbi.nlm.nih.gov/30599804/>
  16. Beh, Shin C.; Masrour, Shamin; Smith, Stacy V.; et al. Clinical characteristics of Alice in Wonderland syndrome in a cohort with vestibular migraine. *Neurology: Clinical Practice*, v. 8, n. 5. 2018. p. 389–396. <https://pubmed.ncbi.nlm.nih.gov/30564492/#:~:text=We%20observed%20several%20rare%20and,AIWS%20and%20VM%20with%20migraine>
  17. Matsuura, Kazuki; Ishikura, Ryoko; Oguri, Masayoshi; et al. Atypical Symptoms in Migraine-Related Alice in Wonderland Syndrome: Expansion of the Phenotype and Reflection on the Pathomechanism. *Yonago Acta Medica*, v. 62, n. 1. 2019. p. 163–165. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6437396/>
  18. Palacio-Sanchez, Leonardo ; Sebastián, Juan. Breve historia del síndrome de Alicia en el país de las maravillas: perspectiva. *Repert. med. cir. ,* 2017. p. 256–257. <https://pesquisa.bvsalud.org/portal/resource/pt/biblio-909789>
  19. Camacho Velasquez, JL; Rivero Sanz, E; Tejero Juste, C; et al. Síndrome de Alicia en el país de las maravillas en patología cerebrovascular. *Neurología (Barc., Ed. impr.)*, v. 31, n. 6. 2016. p. 418–420, 2016. <https://pesquisa.bvsalud.org/portal/resource/pt/ibc-154458>
  20. Farooq, Osman ; Fine, Edward J. Alice in Wonderland Syndrome: A Historical and Medical Review. *Pediatric Neurology*, v. 77.2017. p. 5–11. <https://pubmed.ncbi.nlm.nih.gov/29074056/>
  21. Mastria, Giulio; Mancini, Valentina; Cesare, Marco Di; et al. Prevalence and characteristics of Alice in Wonderland Syndrome in adult migraineurs: Perspectives from a tertiary referral headache unit. *Cephalalgia*, v. 41, n. 5. 2020. p. 515–524. <https://pubmed.ncbi.nlm.nih.gov/33167711/>
  22. Gómez-Sanchez, Daniel; Ros-Cervera, Gonzalo; Pérez-Verdú, Julia; et al. Aura sin migraña o síndrome de Alicia en el País de las Maravillas: Caso clínico pediátrico. *Arch. argent. pediatr.* 2019. p. 34–36. <https://pesquisa.bvsalud.org/portal/resource/pt/biblio-983776>
  23. García-Cabo, C. et al. Alice in Wonderland syndrome as the initial and sole manifestation of ischaemic stroke. *Neurologia (Barcelona, Spain)*, v. 34, n. 7, p. 487–488, 1 set. 2019. <https://pubmed.ncbi.nlm.nih.gov/28081974/>
  24. Blom, J. D.; Nanuashvili, N.; Waters, F. Time Distortions: A Systematic Review of Cases Characteristic of Alice in Wonderland Syndrome. *Frontiers in Psychiatry*, v. 12, 7 may 2021. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8138562/>
  25. Yokoyama, T. et al. A case of recurrent depressive disorder presenting with Alice in Wonderland syndrome: psychopathology and pre- and post-treatment FDG-PET findings. *BMC Psychiatry*, v. 17, n. 1, 27 April 2017. <https://pubmed.ncbi.nlm.nih.gov/28449649/>
  26. Vara, F. J. M. et al. Síndrome de Alicia en el País de las Maravillas e infección por virus de Epstein-Barr. *Pediatr. aten. prim*, v. 21, n. 1139-7632, p. e67–e70, 2019. <https://pesquisa.bvsalud.org/portal/resource/pt/ibc-184588>
  27. Rocha, A. P. et al. Síndrome de Alice no país das maravilhas e reativação de infecção por Epstein-Barr. *Rev. bras. neurol*, v. 55, p. 35–37, 2019. <https://pesquisa.bvsalud.org/portal/resource/pt/ibc-184588>