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ESSAY

Alice in Wonderland Syndrome (AIWS). A reflection

Síndrome de Alicia en el país de las maravillas (AIWS). Reflexión

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Abstract

The Alice in Wonderland syndrome is a rare clinical neurological condition, defined by the presence of perception disorders usually interpreted by the affected patient as rare metamorphosing and depersonalization phenomena. Due to its extremely rare occurrence and its surreal and sometimes psychedelic character, the syndrome has been associated with the phenomena experienced by Alice, the character in the classic and world-famous story by Lewis Carroll.

Resumen

El Síndrome de Alicia en el País de las Maravillas es una condición clínica neurológica de rara aparición, definida por la aparición de alteraciones en la percepción usualmente interpretadas por el paciente que las experimenta, como fenómenos extraños de metamorfosis y despersonalización. Por su naturaleza altamente inusual y su carácter surreal e incluso en ocasiones psicodélico, se ha relacionado al cuadro con los fenómenos experimentados por

el personaje de Alicia, en la clásica y mundialmente reconocida historia de Lewis Carroll.

Introduction

The Alice in Wonderland syndrome (AIWS) is a clinical presentation of distorted body images and/or objects surrounding the subject experiencing the syndrome. Several medical conditions have been associated to this condition, the exact cause of which is yet unknown.^{1,2}

This article reflects on the clinical manifestations of the syndrome, understanding the most frequent clinical characteristics, its etiology, and treatment.

The authors consider that the name of the syndrome is relevant, although the etiology varies and is particularly associated to migraine. Furthermore, there is no other type of headache with the name of a renowned work of literature such as Alice's story. The link between art and medicine has always existed, and it seems that by the middle of the 20th Century, when the syndrome was

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described, it could have been called otherwise, probably an eponym, but during the second decade of the 21st Century it still maintains its initial name. The authors clearly understand that this bond still prevails; despite the classifications developed by experts on different topics, the cosmetic value of a medical condition should not be neglected, because it is an expression of the cultural heritage of mankind.

An elaborate description through clinical practice guidelines or a concrete medical description could hardly convey so eloquently the multiplicity and the exceptional nature of the symptoms experienced by AIWS patients. The very dramatic sensory perception disorders that patients describe fit better in the expansive literary world rather than inside the boundaries of a medical description.

A cardinal alteration in AIWS is the unbalance between the self-representation and/or the perception of the real world. Patients with AIWS experiencing symptoms may have an erroneous perception of their body size or a distortion of the size and shape of the objects around them.^{1,2}

Recently, the data from a systematic review³ showed that between 1955 and 2015, 169 cases of patients with Alicia's syndrome have been reported in the literature, most of them in subjects ≤ 18 years old. Additionally, it was found in a study carried out in Japanese population with 3224 subjects between 13 to 18 years old that occurrence of micropsia and macropsia was 6.5% and 7.3% in males and females, respectively, suggesting that visual illusions in AIWS are not as infrequent as usually believed.⁴⁻¹¹ Nonetheless, it is believed that these cases represent just a small proportion of the actual prevalence of the syndrome, mainly because of the lack of a definition, classification, and adequate diagnostic criteria that are consistent with international parameters, in addition to the lack of reliable epidemiological data accounting for its real magnitude.

Clinical manifestations

Undoubtedly, it could be said that the so called AIWS is a clear example of what used to be defined as cryptogenic—a clinical manifestation of apparently unrelated pleiotropic symptoms, with a secret background, a neurological etiology lying inside the depths of the neural fabric. Over the past 60 years, a total of around 42 somatosensory symptoms have been associated with the AIWS. Typically, the syndrome presents during childhood, which may be considered a precursor of migraine; children seem to be most susceptible to develop migraines in the future, or during early adolescence, but this does not preclude the possibility of adult clinical cases. There is no sex predilection, except for migraine-associated cases that are prevalent in females. In general, the symptoms do not present simultaneously with migraine, but just before or after the migraine episode. The syndrome is characterized by the presence of transient episodes of visual hallucina-

tions and distorted perception.⁵ The principal clinical manifestation is a distorted perception of the body image, where the patient is fully aware of what is going on, with no awareness alteration. Patients are under the impression that different body parts are changing.³

Moreover, the sense of time is also affected; time may seem to pass very slowly or just the opposite, that everything happens in a very short time. Some patients experience visual hallucinations, changes in size, distance, or the position of static objects with frequent distortion of the circumstances around the event. There may be alterations in hearing and tactile perception, and episodes of depersonalization and derealization, somatophycic duality, and felling like levitating. Others experience fear and even terror during the event.^{1,2,6}

The episodes may present several times during the day and last less than 24 hours, with a start and end in most cases. To a large extent, the presentation is episodic and some cases may evolve towards chronicity.^{2,6}

Some findings indicate that metamorphopsias may seem to last for seconds or minutes and will be altered after fixing the eyesight on 1 single object; however, during that perception process, the objects will not be seen as distorted. The explanation may be cerebral asthenopia, interpreted as the fatigability of the perception system.³

Functional magnetic resonance imaging (MRI) studies have identified an occipital hypoactivation and a hyperactivation of the parietal lobe when micropsia occurs.³

Diagnostic aids

Brain computed tomography (CT) and MRI usually show no alterations.^{2,6} The electroencephalogram may present alterations in patients with an etiology of epilepsy.⁷ Single-photon emission CT studies have been conducted, which reveal hypoperfusion of the temporal lobes and around the optic tract and its connections.⁶ Visual evoked potentials show 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. However, further studies are needed to learn about the etiopathogenesis that could explain the findings in the diagnostic aids.^{6,8}

Notwithstanding the fact that AIWS lacks explicit classification criteria, Valença et al⁵ suggested the following diagnostic criteria for AIWS-associated migraine in 2015: 1 or more episodes of body distortions or metamorphopsias; duration < 30 minutes; accompanied by headache or with a history of migraine; and normal MRI, cerebrospinal fluid, and electroencephalogram (abnormal visual evoked potentials).

Etiology

About 166 cases of AIWS have been published in the literature, identifying various types of conditions associ-

Table 1. Conditions and factors associated with the Alice in Wonderland syndrome.

| Type | Disease/factor |
|----------------------------|---|
| Nervous system pathologies | Migraine, temporal lobe epilepsy, trauma-associated encephalopathy, brain tumors, intracranial aneurysms, acute disseminated encephalomyelitis ^{1,4,7,14} |
| Psychiatric pathologies | Schizophrenia, depressive syndrome, derealization/depersonalization disorder ⁴ |
| Infectious diseases | Lyme's disease, Epstein-Barr virus infection, Coxsackie virus infection, H1N1 influenza virus infection, cytomegalovirus infection, Strep Pharyngo-amygdalitis, varicella ¹⁰ |
| Drugs | Montelukast, Dextrometorphan, Topiramate, Risperidone ⁴ |
| Psychoactive substances | Marihuana, LSD, cocaine, amanita muscaria, extasis ⁴ |

Source: Adapted from^{1,4,7,10,14}.

ated with the syndrome. The most frequent are migraine (27.1%), followed by infections (22.9%), mainly associated with Epstein-Barr virus (15.7%). Additionally, in declining order of prevalence, there are brain injuries, drugs, psychotropic substances, psychiatric disorders, and epilepsy, inter alia^{1,4,7-11} (Table 1).

With regards to area of the brain involved, it has been thought that the manifestations are the result of parietal lobe involvement.^{1,6,9}

Migraine and Alicia's syndrome

Migraine has been described as the most frequent etiology of the above-mentioned visual alterations. Edward J. Fine gives a possible explanation as to why migraine may result in episodes of visual alterations. Migraine may be triggered by various factors including stress, red wine, aspartame, smoked food or dark drinks, chocolate, skipping one important meal in a day (breakfast, lunch, or dinner), inter alia. Apparently, what happens with migraine is the dissemination of a depolarization wave of brain cells along the cerebral cortex. The depolarization caused by the glial cells results in the extracellular release of potassium and calcium ions, nitric oxide, and arachidonic acid, leading to the activation of axonal meningeal nociceptors. These nociceptors are part of the trigeminal nerve, which, in addition, to innervating part of the face, has connections to the thalamus and presents thalamic projections towards the sensory cortex. Due to these mechanisms and connections, in addition to producing headaches, migraine may result in sensitive alterations. For instance, visual alterations in the AIWS.¹

In a study conducted by Smith et al, including children between 8 and 18 years of age, 16 subjects were invited to participate, but only 9 of them gave their consent to conduct the trial. The results showed that the mean age for the onset of visual alterations was around 8.4 years, whereas the headache episodes began at approximately 9.4 years. In 4 children, the onset of visual symptoms was identified before the occurrence of headache and in 2

children the visual symptoms began simultaneously with the episode of headache, and finally in 3 other children, the visual symptoms presented after the end of the headache spell.¹⁴

Treatment

It has been said that most of the cases of AIWS are benign, in as much as either spontaneously or with adequate treatment, there is total remission. This claim is further supported by the fact that the syndrome does not present only in people with underlying or associated conditions, but it may also develop in the general population. In contrast, the clinical manifestation of AIWS may be relapsing and frequent during the active phases of chronic associated pathologies that require adequate long-term treatment. Therefore, in most cases, therapy is helpful to treat the associated underlying condition in these patients. For instance, antiepileptics and antibiotics could be the right choice to treat epilepsy or infectious diseases, respectively.³ Similarly, it has been found that electroconvulsive therapy and transcranial magnetic stimulation have resulted in positive outcomes in patients receiving these therapies. In the case of patients with migraine, an adequate prophylactic treatment, together with proper diet, results in considerable improvement.²

Prognosis

The prognosis depends on the etiological factor involved, but in most cases, is good. Episodes tend to decline in frequency and intensity as time progresses.^{2,6}

Weidenfeld and Borusiak¹⁰ report a series of cases of 9 children diagnosed with AIWS between 2003 and 2008, and they were followed to assess the long-term consequences of the syndrome. The results of this study concluded that in accordance with the literature, AIWS is a benign condition in most cases and it does not require specific treatment or long-term follow-up. However, there is the possibility of an occasional occurrence of symptoms, and

before taking for granted the benign nature of the symptoms, acute medical conditions must be ruled out, including encephalitis, epilepsy, or cerebrovascular accidents.¹⁰

Recent studies have identified a link with depression, and pre and post-treatment positron emission tomography (PET) changes have been documented, suggesting a biological substrate in the genesis of the condition. In a case reported in Japan, a 63-year-old male, with major depressive disorder, showed metabolic alterations in the association cortexes, particularly the occipital, frontal, and parietal. The imaging abnormalities resolved after treatment, suggesting a common etiology and a biological substrate shared with depression, particularly with regards to the alterations in the prefrontal and visual cortexes.¹¹

Other studies have found similar alterations in images of a region named the temporo-parieto-occipital *carrefour*. This anatomic site is the crossroads of the temporal, parietal, and occipital regions that make up the somatosensory information with the visual afferences and may explain the sensory-perceptive alterations present in the syndrome.⁴

Conventional MRI imaging usually do not show any structural alterations, as indicated by Liu et al¹² in a review of 48 cases of children with AIWS that presented characteristic visual-perceptive symptoms.

Optic coherence tomography (OCT) shows no alterations, as observed in the case of a 19-year-old patient with AIWS, associated with Epstein-Barr virus infection.¹³

Lerner and Lev-Ran described in a case report a 26-year-old patient who during an LSD intoxication presented with episodes of visual illusions in the form of macropsia, micropsia, pelopsia, and teleopsia. These distortions occurred when the subject observed moving objects, stationary objects, human beings, and inert objects. Although the individual stopped using LSD, the optical illusions persisted and decided to visit a psychiatrist. The patient refused pharmacological treatment, but continued with control visits to the psychiatrist. Finally, the illusions vanished progressively over the course of 1 year.¹⁵

Obviously, the name of the syndrome is attributable to fantastic experiences described in the story as lived by Alice; Todd⁹ and other authors reviewed the documents that clearly indicate that the author, Lewis Carroll, suffered from migraine and consider that eventually the author himself experienced similar conditions to those of syndrome herein discussed.

So the authors suggest that the profound interest of many doctors to describe a condition may lead to the discovery and intertwining of associations never imagined, which could offer the nosological characteristics of a pathological condition. Such nosological traits of this neurological condition may be so strong that, despite any future updates to pathological conditions, this name will hopefully persist for many more years.

Once again, this is the enduring bond among art, science, and medicine.

The authors believe it is important to stress the relevance of this condition, which, although rare, if the physician treating the patient is not familiar with the syndrome, the diagnosis may be missed, particularly if the doctor believes that this may be a manifestation of migraine in childhood.

The pathophysiology of AIWS is a clear example of the range of manifestations arising from any nervous system pathology, and, in particular, how our senses may be affected and result in an absolutely surreal sensory-perceptive experience that generates a lot anxiety in patients.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of interest

No conflicts of interest to disclose.

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