Alice in Wonderland Syndrome

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ABSTRACT
In this paper, we investigate the so-called “Alice in Wonderland syndrome” (AIWS) disorder by first giving an introduction to this disorder and then providing more information on the history of this disease. In the next section, we look at the symptoms together with various examples with their similarities and exceptional signs as well as rare long-term studies which are very useful for physicians and can contribute to a better clinical diagnosis. Afterwards, the diseases that are associated with this syndrome are named and being aware of such diseases will not only provide new research topics for physicians, but also help them better treat and prevent them from giving other irrelevant treatment methods. Furthermore, besides the associated diseases other factors related to this syndrome is discussed. In addition, the existing diagnostic and treatment methods together with various examples are investigated. Finally, the results of some of the previously done studies are discussed based on their categories. In this article, we encounter some exceptional cases that according to their author are investigated for the first time, and this review provide accurate information which are useful for diagnosis and treatment as well as further research ideas.

SEARCH STRATEGY
This disease is an extremely rare disease with few limited studies devoted to its investigation, such that less than 100 citations are retrieved in search engines like Pubmed using titles, abstracts and “Alice in wonderland” as the keyword. Even though these searches were done without typing the words “syndrome” or “disease”, many of the retrieved citations were either irrelevant papers or very simple case report studies.

RESULTS
We reach different conclusions in every section of this paper. For instance, in the introduction and history we conclude that this syndrome is in fact named after the novel with the same name. Discussing the symptoms we notice that this disorder can manifest itself without migraine headaches or even without previous illness or at any certain point. Discussing the diseases associated with this syndrome, we conclude that it can be associated with a wide range of disorders some of which have been reported for the first time in papers by different authors and further research may contribute in finding other new AIWS-associated disorders. In addition, the effectiveness of treatments, differences in diagnostic
INTRODUCTION

Alice in Wonderland syndrome (AIWS) is a rare cluster of CNS symptoms [1] and a rare clinical disorder [2] characterized by bizarre perceptions of changes in size and shapes of patient's body image and illusions of changes in the forms, dimensions, and motions of objects [3] and reciprocal position of objects and their colors [4]. These changes in forms of objects or subjects [metamorphopsia] that may appear smaller [micropsia] or larger than normal [macropsia] [5,6] which with time is associated with enlargement of surrounding environment [8] [6]. It must be mentioned, that in some cases objects may appear small and distant [teleopsia], or large and closer [peliopsia] [7]. This rare and easy-to-diagnose syndrome that mainly seems to affect children can be defined in those with Epstein-Barr virus infection [2]. Epstein-Barr virus infection may include visual symptoms as the first or only signs of disease [8]. This syndrome is usually associated with migraine headaches as well as other viral infections [9], and cases if AIWS have been linked to infectious mononucleosis [6].

HISTORY and NOMENCLATURE

In 1955, John Todd (1914–1987), a British psychiatrist described unique symptoms of this syndrome that often occur with depersonalization and derealization to be closely associated with migraine and epilepsy [6,10]. Although Todd's report was the most influential, Lippman provided an earlier definition in 1952 and as a result he is considered the first to have reported this syndrome. Migraine sensation is a transient neurologic sign of this syndrome that is usually associated with visual fields and occurs before the headache phase. Todd named AIWS for the perceptual disorder of altered body image experienced by the protagonist in the novel Alice's Adventures in Wonderland (1865). This novel is written by Lewis Carroll (the pseudonym of Reverend Charles Lutwidge Dodgson (1832-1898)) that is possibly based on Dodgson's own migrainous experiences before 1865 [10,11]. The story is about Alice Liddell and her two sisters after he spun a tale about a long and strange dream that the fictional Alice had on a warm summer day [3]. In the story, Alice followed a talking rabbit down a rabbit hole and then experienced several dramatic changes in her own body size and shape, such as shrinking to 10 inches high, growing unnaturally large, and tall but not any wider. In Lippman's paper, one of the patients reported feeling short and wide as she walked, and referenced Alice's Adventures in Wonderland in regard to her body image illusions [10]. Having explained all the above, we are now familiar with the history, the story, and the similarities that exist between the novel and the name of this disease and the fact that it is based on the author's own migrainous experiences.

SYMPTOMS

The symptoms of AIWS include, paroxysmal body disturbances [obligatory core symptom of AIWS], as well as depersonalization, derealisation, visual illusions and disorders of time perception (Facultative symptoms of AIWS) [11]. Migraine aura is said to be a transient neurological symptom that most frequently involves the visual fields and occurs before the headache phase. Aura symptoms include the perception of flashing lights that starts in the center of vision and expand in jagged patterns out into the periphery. Symptoms may be somatosensory, such as numbness and tingling in the lips or fingers. They may also involve a significant alteration of the perception of space and time (the “Alice in Wonderland” syndrome) [5]. In some studies, migraine aura is not present initially but later will manifest itself. For example, a 37-year-old woman had had a migraine without aura since puberty and in the months of follow-up, she experienced several episodes of unusual auras preceding typical migrainous headache. The aura lasted about 30 minutes and consisted in the feeling of lengthening of the trunk and of the four limbs, associated with a sensation of well-being [12]. In one study, a 7-year-old boy with AIWS associated with Lyme disease presented with metamorphopsia and visual hallucinations in the absence of previous bites or other signs of Lyme disease who never developed clinical seizures, and his electroencephalograms did not indicate any epileptic activities. This patient had no history of migraine. Cranial magnetic resonance imaging produced normal results. Lyme serology tested positive in both serum and cerebrospinal fluid.

In order to better understand the symptoms of AIWS, we review two studies in which the patients describe their similar symptoms.

In one study a 20-year-old boy is investigated who experienced frequent prolonged attacks [≥ 7 days] of distortions of shape, size or position of objects or subjects at 17. He explains:

“Quite suddenly, objects appear small and distant (teleopsia) or large and close (peliopsia). I feel as I am getting shorter and smaller “shrinking” and also the size of persons are not longer than my index finger (a lilliputian proportion). Sometimes I see the blind in the window or the television getting up and down, or my leg or arm is swinging. I may hear the voices of people quite loud and close or faint and far. Occasionally, I
experience attacks of migrainous headache associated with eye redness, flashes of lights and a feeling of giddiness. I am always conscious to the intangible changes in myself and my environment” [7].

In the next study, a rare case of aura without headache is reported. This case is an 8-year-old girl who experiences one to three brief episodes a day during one month who explains:

“I saw things as little and remote, sometimes they moved; one day I saw my sister’s books turning bigger, and another day my father getting little as a doll; sometimes my doll’s leg swunged, or the blind of the window got up and down.”

Later these attacks spaced out to one each to days for another two weeks. With no previous episodes of headache, these start two days after the visual distortions disappeared, with clinical features of migraine in maternal line, and no previous trauma, epilepsy, drug ingestion or psychiatric disorders. Clinical examination, cranial RMI, and EEG were normal. Authors mentioned that although AIWS was described as a migraine aura, it is usually brief, and it is exceptional that it lasts longer than a week and they think this is the first description in a pediatric patient [13].

Now we look at general characteristics and the obtained results found in long-term studies and it is worth mentioning that the following data are rare [14].

First, we investigate a study done on 20 patients under the age of 18 years old diagnosed with AIWS from January 1995 until February 2010 that evaluate the, electrophysiological, clinical, etiological and natural evolution in children with AIWS.

The average of age of the diagnosis was 9.5 ± 3.8 years (range: 4-16 years). The disease appeared in an acute way in 85% and progressive in 15% of the cases. 90% of patients had micropsias and/or macropsias. 85% distortion of the form of the objects, 80% displacement of objects, 45% disturbances of body image, 45% acceleration of the time, 30% sensation of unreality and 95% of them had many episodes a day that lasted less than 3 minutes in 90% of them. The result of the Electroencephalogram was found to be abnormal in 11 cases, in one case epileptic foci were seen (left temporal) and in 10 cases posterior slow waves were noticed. The neuroimaging tests were normal in all the patients. The visual evoked potentials were found in 7 children of whom five showed higher amplitude in evoked potentials and two of the children had normal potential. The infectious etiology was found in nine cases. 80% did not have recurrence [15].

Next we investigate a study done between 2003 and 2008 on nine boys aged 6 to 11 years old who were contacted for a long-term follow-up study with a mean follow-up of 4.6 years. During this time all children were in good general and mental health and symptoms had ceased within weeks or months. In two patients, episodes of metamorphopsia returned after a symptom-free latency of 3 years and 1 year, respectively. Five children had a family history of migraine or epilepsy. In one case, the father of one of the boy was reported to have experienced similar symptoms in his childhood [14].

**RELATED DISEASES**

In order to explain the importance of this topic we quote a sentence from one of the studies done:

“The clinician’s awareness of the existence of this syndrome in H1N1 influenza might save the child from undergoing extensive diagnostic procedures [16].”

Alice in Wonderland syndrome is associated with migraine and epilepsy [17] and this disorder which rarely occurs in adults is mainly linked to migraine with aura and epilepsy [12]. In conclusion of another study the main etiology of this syndrome was attributed to Epstein-Barr virus infection [13] [15]. Now we are going to name the remaining related diseases that have been mentioned in other studies.

In this article, we pointed out that this syndrome might be in association with various infections. This disorder is as much discussed in association with infectious mononucleosis as it is with other clinical presentations such as migraine, epilepsy and use of hallucinogenic drugs [4]. In many studies, the association between AIWS and infectious mononucleosis is emphasized [18] and this syndrome is said to be a presenting symptom of infectious mononucleosis [19].

Now we look at the studies that attribute this syndrome to influenza. In one study, there was possible association between AIWS and influenza-A infection [20]. In another study, it was reported that AIWS is caused by the 2009 Pandemic H1N1 Influenza-A Virus [21]. In another study, AIWS was also said to be linked to H1N1 influenza [16]. We now look at two different cases of AIWS that were associated with migraine. In one study it is reported that a 20 years-old male according to the author showed AIWS associated with abdominal migraine. He started to have prolonged attacks of abdominal colic at the age of ten [7]. In another study, cases of AIWS with Juvenile Migraine were reported [22].

Now let us look at other diseases that are reported to be associated with AIWS. In one study, AIWS was said to be associated with Lyme disease [23]. In a different study AIWS was reported to be caused by Coxsackievirus B1 [24]. The relationship between AIWS and varicella was investigated in another research paper [25]. In other studies, similar symptoms of AIWS including, visual metamorphopsia is defined in patients with migraine, epilepsy, intoxication due to hallucinogenic drugs, schizophrenia, hyperpyrexia, and cerebral lesions, as well as in the course of IM [26]. In one
of the studies, the case of a 17-year-old girl with migraine without aura who showed an AIWS repeatedly while on topiramate treatment [27] was reported and in another paper AIWS developed one week after topiramate treatment in order to prevent migraine [28]. In a different research paper, the probable relationship between AIWS and the use of montelukast was proposed [29].

**Treatment and diagnosis:**

Let us now investigate the brain areas involved in this disease together with the diagnosis and treatment methods. Nuclear medicine techniques are able to demonstrate changes in cerebral perfusion and may be used to detect abnormal cerebral areas in patients with AIWS [6]. In one research paper these findings were obtained using Technetium-99m hexamethylpropyleneamine tomodraphy, SPECT brain scans in acute stage of AIWS. In acute stage of AIWS the following results were obtained:

The decreased cerebral perfusion areas in all patients were near the visual tract and visual cortex. All involved some regions of the temporal lobe. In most cases with AIWS, the EEG, CT, and MRI are unable to determine the precise pathologic areas, but a SPECT brain scan may demonstrate abnormal perfusion areas and explain the clinical presentations [30].

In results of another study on a 10-year old girl with AIWS is as follow:

MRI demonstrated transient T2 prolongation and swelling of the cerebral cortex, especially at the bilateral temporal lobes, bilateral cingulate gyrus, right upper frontal gyrus, bilateral caudate nucleus, and bilateral putamen, whereas CT showed no abnormalities. Transient abnormal lesions were occasionally reported in patients with EB virus encephalopathy/encephalitis who presented visual illusions and psychotic reactions, although the diagnosis of AIWS was not described [31].

Epileptologic and experimental data suggest that the AWIS is associated with a transient dysfunction of associative somatosensory areas in the parietal cortex [12]. The active experience of micropsia in viral-onset Alice in Wonderland syndrome reflects aberrant activity in primary and extrastriate visual cortical regions as well as parietal cortices [32].

**In one study, the treatment method of a 20-year old male with abdominal migraine and AIWS is explained as follow:**

Treatment with valproate resulted in marked improvement of all clinical and neurophysiological abnormalities [7]. In another study, a 7-year old boy with AIWS associated with Lyme disease was treated with intravenous ceftriaxone for 3 weeks, with complete resolution of signs. According to the author, this case report is the first neuroborreliosis presenting as AIWS with complete resolution of findings after intravenous antibiotic treatment.

**In another research paper, in order to treat AIWS and verbal auditory hallucinations the following methods were used:**

Semi-structured interviews were used to assess symptoms, and functional MRI (fMRI) was employed to localize cerebral activity during self-reported VAs (Verbal Auditory Hallucinations). Treatment consisted of repetitive transcranial magnetic stimulation (rTMS) at a frequency of 1 Hz at T3P3, overlying Brodmann’s area 40. This case indicates that VAs and metamorphopias in AIWS are associated with synchronized activation in both auditory and visual cortices [32].

**CONCLUSIONS**

With respect to EBV serological tests in children with AIWS, one paper considered that all children presenting AIWS symptoms should undergo serological testing for Epstein Barr virus infection [9] and another paper suggested that every young child presenting clinical features of AIWS should undergo serological testing for Epstein Barr virus infection [33]. However, in a different study it is recommended that all the patients who show clinical features of AIWS should undergo serological testing for Epstein Barr virus infection [8].

Regarding the probability of recurrence of this syndrome one study stated that AIWS is without recurrence in most of the cases [15]. Another paper suggested that occasional recurrence of symptoms is possible [6]. It has been suggested to define the AIWS by the presence of visual rather than somesthetic perceptual disturbances [1].

**REFERENCES**


