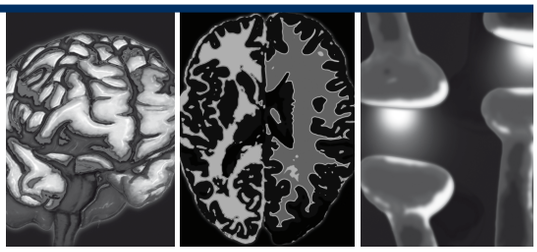
SPECIAL REPORT



An overview of the symptoms and typical disorders associated with Alice in Wonderland syndrome

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Practice points

- Alice in Wonderland syndrome is characterized by the sudden onset of distorted visual perceptions, such as metamorphopsia, allesthesia and teliopsia, unexplained by a ophthalmological pathology.
- Most frequent etiologies are migraine headaches and epilepsy.
- Patients are often aware of their own distortions, differentiating this condition from psychoses in which insight is usually impaired.
- Symptoms typically resolve with treatment of accompanying pathology.

SUMMARY The Alice in Wonderland syndrome refers to a set of symptoms characterized by perceptual distortions, such as visual distortions (i.e., metamorphopsia), body image and time distortions. The Alice in Wonderland syndrome has been described consistently over the past five decades in various cultural settings. Migraine headaches and epilepsy were the etiologies first described and most frequently reported in the literature; however, infectious, neurological, toxic and psychiatric causes have also been reported. Although little is known regarding the specific pathophysiological pathways, dysfunctions of the NMDA neurotransmission and inflammations, as well as edemas of cerebral regions close to the visual pathways may be implicated.

In Lewis Carroll's Alice in Wonderland's opening scene [1], Alice drank from a bottle that caused her to shrink: *"What a curious feeling!" said Alice; "I must be shutting up like a telescope."* Later, eating a piece of cake made her grow: "*Curiouser and curiouser" cried Alice. "Now, I am opening out like the largest telescope that ever was! Goodbye feet!*"

Although Lippman published the first clinical reports of a syndrome, including symptoms resembling these unusual body image distortions, in a paper reporting on seven migraine patients [2], it was not until 1955 that another author, Todd, named the syndrome after Lewis Carroll's novel [3]. In his publication, Todd proposed grouping the symptoms experienced

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by Alice ("hyperschematia, hyposchematia, derealization, depersonalization and somatopsychic duality") together with other symptoms that often accompany them such as "illusory changes in the size, distance, or position of stationary objects in the subject's visual field, illusory feelings of levitation; and illusory alterations in the sense of the passage of time" [3]. Todd also noted that patients are often aware of their own distortions, differentiating this condition from psychoses in which insight is usually impaired.

To date, visual distortions or metamorphopsia are still the hallmarks of Alice in Wonderland syndrome (AIWS); however, other symptoms frequently accompany them. These include: an inability to recognize faces (prosopagnosia), illusions in which objects appear to be smaller (micropsia) or larger (macropsia) or in which people appear to be miniscule (lilliputianism) and objects transposed from one point of view to another (allesthesia). Finally, in some cases, symptoms of dissociation, such as depersonalization (the feeling of watching oneself act, while having no control over a situation) and derealization (the alteration in the perception or experience of the external world so that it seems unreal), occur concurrently with the classic visual distortions.

While the first cases of AIWS were described in patients with migraine headaches or epilepsy (in his description of the syndrome, Todd reported six cases of AIWS associated with migraine and epilepsy), in the five decades following Lippman and Todd's descriptions, cases of AIWS involving other etiologies have been regularly reported in the literature. The present article aims to review the literature available on the etiologies of AIWS.

Search method & characteristics of the reported cases

A search was conducted on MEDLINE using the key words 'Alice in Wonderland Syndrome' and 'Alice in Wonderland'. Further publications were identified from the reference list of publications selected, while review papers were excluded from our study [4–6]. Including Lippman and Todd's papers, the search yielded a total of 33 publications examining AIWS. All publications were either single case reports (n = 21) or case series (n = 10).

In total, from 1952 to 2012, 86 cases of AIWS were reported in the literature. The youngest patients were 4 years old [7,8], and the oldest was 74 years of age [9]. The cases reported reveal no gender imbalance (n = 47; females: 55%). The shortest duration was a few days [10], while the longest syndrome described lasted several years [11].

The vast majority of descriptions had either a neurological or an infectious etiology (n = 31; 36% and n = 35; 41%, respectively); only three papers described patients with a psychiatric disorder [9,12,13]. Interestingly, publications emanated from 12 different countries belonging to four different continents (Africa, America, Asia and Europe). All the relevant studies are reported in **Table 1**.

Etiologies

■ Neurological etiologies

Migraine headaches

Migraine was the first etiology identified for AIWS, as reported above [2,3]. In line with these two first publications, Golden reported the case of two children with recurrent episodes marked by an impaired sense of time, altered body image and visual hallucinations [14]. Both children had family and personal histories of migraine. Kew *et al.* also reported the case of a patient with a long history of migraine [15]. The patient experienced somesthetic auras with and without headaches. The aura was of her body shrinking (microsomatognosia) and a gross magnification of both hands: "I suddenly get a feeling that my hands are huge and I mean huge: ginormous" [15]. The authors observed that in general patients were reluctant to discuss these symptoms, as contrary to visual hallucinations, they were usually aware that the distortions of AIWS were not real. A fifth report detailed the case of a migraine patient with abdominal colic and AIWS [16]. The patient irregularly experienced attacks of abdominal colic associated with autonomic manifestations (e.g., nausea, abdominal flushing, pallor, tachycardia and diarrhea) and experiences of distorted shape, size and position of objects or subjects. The author highlighted that in two cases the migraine phenomena disappeared after antiepileptic treatment (valproic acid) and may have resulted from the same neurophysiological process as the migraine headache.

Epilepsy

Epilepsy has also been identified as an etiology of AIWS. In his landmark publication, Todd diagnosed AIWS in association with migraine–epilepsy in two cases [3]. The two patients (two women, 17 and 32 years of age),

Table 1. Summary of the studies examining Alice in Wonderland Syndrome between 1952 and 2012.

Study (year)	Country	Patients (n; population)	Type of publication	Symptom(s)	Etiology	Symptoms duration	Ref.
Lippman (1952)	USA	n = 7 (six women, one man, aged 23–64 years)	Case series	Micropsia and macropsia	Migraine	–	[2]
Todd (1955)	UK	n = 6 (five women, one man, aged 17–43 years)	Case series	Micropsia, macropsia, teliopsia, peliopsia, giddiness, sensation of being 'split', derealization, depersonalization, sense of time slowing down, paresthesia, headaches and palpitations	One case unknown, three cases of migraine, two cases of migraine–epilepsy	–	[3]
Copperman (1977)	USA	n = 3 (one boy, aged 9.5 years, two girls, aged 17 and 18 years)	Case series	Derealization, macropsia, micropsia, hyperacusis, tinnitus and blurring of vision	Mononucleosis infection	Intermittent symptoms for 2 months	[18]
Golden (1979)	USA	n = 2 (one girl, aged 11 years, one boy, aged 1 year)	Case series	Metamorphopsia, attacks of impairment of time sense, body image and visual analysis of the environment	Juvenile migraine	–	[14]
Sanguineti *et al.* (1983)	Italy	n = 1 (32-year-old male)	Case report	Metamorphopsia, perception of objects rapidly moving backwards and forwards, derealization, miscalculation of the position of objects and blurring of vision	Mononucleosis infection	–	[19]
Lahat *et al.* (1990)	Israel	n = 1 (6-year-old girl)	Case report	Metamorphopsia, headaches and anxiety	Mononucleosis infection	6 weeks	[20]
Liaw and Shen (1991)	China	n = 4 (two girls, two boys, aged 4–9 years)	Case series	Micropsia, macropsia, lilliputianism and allesthesia	Mononucleosis infection	1 week–3 months	[38]
Cinbis and Aysun (1992)	Turkey	n = 1 (7-year-old girl)	Case report	Micropsia	Mononucleosis infection	6 months	[39]
Wang *et al.* (1996)	Taiwan	n = 1 (4-year-old boy)	Case report	Metamorphopsia, micropsia, macropsia and illusional symptoms (e.g., interpretation of a wire for a snake)	Coxsackievirus B1 infection	1 year	[7]
Mizuno *et al.* (1998)	Japan	n = 1 (54-year-old male)	Case report	Metamorphopsia and lengthening and shortening of time experience	Major depressive disorder	3 months	[12]
Kew *et al.* (1998)	UK	n = 1 (52-year-old woman)	Case report	Headaches with somesthetic auras, micropsia and macropsia	Migraine	Several years	[15]
Kuo *et al.* (1998)	Taiwan	n = 4 (three girls, one boy, aged 3–8 years)	Case series	Metamorphopsia and visual hallucinations	Two cases of mononucleosis infection, one case with abnormal EEG, one case unknown	5–13 days	[10]
Takaoka and Takata (1999)	Japan	n = 1 (46-year-old male)	Case report	–	Side effects of syrup containing dihydrocodein phosphate and dimethylphedrine hydrochloride	More than 3 years	[11]

–: Not applicable.

Table 1. Summary of the studies examining Alice in Wonderland Syndrome between 1952 and 2012 (cont.).

Study (year)	Country	Patients (n; population)	Type of publication	Symptom(s)	Etiology	Symptoms duration	Ref.
Lahat *et al.* (1999)	Israel	n = 5 (three girls, two boys, aged 10–13 years)	Case series	Micropsia, macropsia, erythropsia and polyopia	Mononucleosis infection	4 or 6 weeks	[21]
Perez-Mendez *et al.* (2001)	Spain	n = 1 (6-year-old boy)	Case report	Macropsia	Mononucleosis infection	2 days	[40]
Takaoka *et al.* (2001)	Japan	n = 1 (22-year-old woman)	Case report	Déjà vu, delusional misidentification syndromes, micropsia, macropsia, allesthesia and hallucination	Abuse of toluene-based solvent	1 year	[26]
Zwijnenburg (2002)	The Netherlands	n = 1 (9-year-old girl)	Case report	Micropsia, macropsia and headaches	Epilepsy	2 days	[17]
Häusler *et al.* (2002)	Germany	3/48 (unclear from article)	2-year prospective study	Metamorphopsia	Reactived mononucleosis infection	6 months	[41]
Evans (2006) and Evans and Rolak (2004)	USA	n = 2 (women aged 27 and 31 years)	Case series	Micropsia, macropsia, derealization and headaches	One case of migraine, one case of side effect with topiramate	–	[28,29]
Gencoglu *et al.* (2005)	Turkey	n = 1 (7-year-old girl)	Case report	Micropsia and macropsia	Viral infection other than Epstein–Barr virus	–	[32]
Corral-Caramés *et al.* (2009)	Spain	n = 1 (8-year-old girl)	Case report	Micropsia	Migraine	3 weeks	[42]
Hamed (2010)	Egypt	n = 1 (20-year-old male)	Case report	Micropsia, teliopsia, associated with abdominal colic and headaches	Migraine variant with abdominal colic	–	[16]
Brumm *et al.* (2010)	USA	n = 1 (12-year-old boy)	Case report	Teliopsia, micropsia, with phonophobia and photophobia	Migraine	–	[31]
Bui *et al.* (2010)	France	n = 1 (74-year-old male)	Case report	Micropsia	Major depressive disorder	45 days	[9]
Jürgens *et al.* (2011)	Germany	n = 1 (17-year-old girl)	Case report	Nocturnal macropsia	Adverse drug reaction of topiramate	3 months	[27]
Augarten and Aderka (2011)	Israel	n = 1 (11-year-old girl)	Case report	Micropsia, macropsia, sense of time slowing down and teliopsia	H1N1 viral infection	3 days	[23]
Weidenfeld and Borusiak (2011)	Germany	n = 9 (boys aged 6–11 years)	Case series	Micropsia, macropsia, diplopic images and panic or agitation	–	Two cases with reappearance of symptoms after >1 year	[43]
Nakaya *et al.* (2011)	Japan	n = 1 (5-year-old girl)	Case report	Micropsia and macropsia	H1N1 viral infection	2 months	[22]
Losada-Del Pozo *et al.* (2011)	Spain	n = 20 (boys and girls aged 4–16 years)	Retrospective study	Micropsia, macropsia, derealization and acceleration of the time	Nine cases of viral infections (five mononucleosis infections), eight cases of migraine, one case of epilepsy, one case with dextrometrophan and one case with cannabis	–	[8]

–: Not applicable.

Table 1. Summary of the studies examining Alice in Wonderland Syndrome between 1952 and 2012 (cont.).

Study (year)	Country	Patients (n; population)	Type of publication	Symptom(s)	Etiology	Symptoms duration	Ref.
Blom *et al.* (2011)	The Netherlands	n = 1 (36-year-old woman)	Case report	Micropsia, macropsia, allesthesia, verbal auditory hallucinations, déjà vu experiences, time distorsions and intuitive feeling of a 'presence'	Schizoaffective disorder	1 year	[13]
Binalsheikh *et al.* (2012)	USA	n = 1 (7-year-old boy)	Case report	Metamorphopsia and auditory hallucination	Lyme disease	3 weeks	[24]
Bayen *et al.* (2012)	France	n = 1 (37-year-old woman)	Case report	Teliopsia and macropsia with headaches	Migraine	–	[44]

–: Not applicable.

had a history of migraine associated with metamorphopsia. EEG data showed a paroxysmal dysrhythmia, especially in the temporal lobes. More recently, Zwijnenburg *et al.* also reported a case of AIWS in a 9-year-old girl resulting from frontal cortex epilepsy [17]. Over 4 days, the patient presented with short attacks consisting of headaches, anxiety and symptoms of AIWS. Treatment with propranolol for migraine did not improve her condition. Two intericteral EEGs revealed intermittent abnormalities (low-voltage spikes and spikewave complexes) exclusively at the right-frontopolar electrode. The seizures disappeared after treatment with the anticonvulsant, valproic acid. A similar case was later described in which a 14-year-old girl experienced derealization, micropsia and macropsia associated with headaches [8]. EEG recordings showed posterior slow waves in the left hemisphere and further investigation identified a left temporal posterior foci. Both clinical symptoms and EEG abnormalities subsided with anticonvulsive medication. These findings suggest the implications of epilepsy in AIWS, however, because of similarities between migraine headaches and epilepsy, a migraine etiology cannot be ruled out.

Although to date, no other neurological etiologies have been reported in the literature, some authors have argued that in patients presenting with hallucinations or metamorphopsia, the presence of an organic etiology such as cerebral tumor, central nervous infection, traumatic brain injury or cerebral aneurisms should be investigated [3,17].

■ Viral etiologies

The association between AIWS and Epstein–Barr infection was first published by Copperman in 1977 [18]. He described three patients, one preadolescent male and two adolescent females, with classical symptoms of mononucleosis infection with asthenia, enlargement of the lymph nodes or spleen and biologic abnormalities (increase in lymphocyte concentration and a positive test for mononucleosis infection), followed by perceptual defects concerning the size, position and distance of objects. After examining a similar case, Sanguineti *et al.* suggested that patients be tested for infection prior to psychiatric diagnosis [19]. Moreover, Lahat *et al.* noted that metamorphopsia may appear before the onset or after the resolution of all mononucleosis infection symptoms [20], the duration of the visual illusions ranged from 2 weeks to 7 months.

In support of a viral etiology, Losada-Del Pozo *et al.* recently found that five out of 20 cases of AIWS were associated with the Epstein–Barr virus [8]. In these viral etiologies, patients most frequently experienced micropsia or macropsia. In another study, Lahat found that children with AIWS and infectious mononucleosis displayed visual evoked potentials of amplitudes similar to those of migraine patients, suggesting that mononucleosis infection and migraine may share a common physiopathologic pathway with AIWS [21].

Recent publications report additional cases of AIWS caused by viral infection, including the Coxsackie B1 enterovirus and H1N1 influenza virus [7]. Wang *et al.* reported the case of a 4-year-old boy with intermittent fever, cough, abdominal pain, watery diarrhea and hepatosplenomegaly associated with visual aberrations (perception of the wall moving backward and forward rapidly and change of his parents' body image in size) [7]. Biologic and serologic tests

identified Coxsackie virus B1 in cerebrospinal fluid and rectal swab cultures. The authors noted that Coxsackie B1 infection was most often asymptomatic, but that neurological symptoms, when they did occur, more often included aseptic meningitis, encephalitis, paralysis, Guillain–Barré syndrome, transverse myelitis, cerebellar ataxia or peripheral neuritis than AIWS did.

Recent case reports suggest the possibility of other viral etiologies. Two publications have reported cases of AIWS associated with the H1N1 virus in both a 5 and 11-year-old girl [22,23]. The two girls presented both metamorphopsia and influenza symptoms, which disappeared spontaneously after a few months. Similarly, Losada-Del Pozo *et al.* identified several cases in which cytomegalovirus and varicella zoster virus were involved in separate, similar cases of AIWS [8].

Bacterial infection may also cause AIWS. Until recently, Lyme neuroborreliosis was known to induce headache, emotional lability and disturbances in sleep, concentration and memory, although not AIWS. In a recent publication, Binalsheikh *et al.* reported a case of Lyme disease presenting with micropsia, macropsia and auditory hallucinations without headaches, suggesting the presence of AIWS [24].

■ Psychiatric etiologies

Depressive disorders have also been described in conjunction with AIWS in two publications [9,12]. The first was a case report of a 54-year-old patient with time and body-image distortions, metamorphopsia and a depressive disorder [12]. In the second publication, Bui *et al.* reported the case of a man with major depressive disorder who, 10 days after admission, complained of body distortions [9]. The patient achieved remission of AIWS and depressive symptoms after five electroconvulsive therapy sessions. Cotard's syndrome, which includes delusions ranging from the belief that one has lost organs to the conviction that one is dead, is usually associated with severe depression [25]. It has therefore been suggested that AIWS in the context of depressive disorders may be a variant of this syndrome [9]. More generally, it could be argued that AIWS occurring during a major depressive episode may actually represent psychotic features accompanying the mood disorder.

Psychotic symptoms include disturbances of thought, visual perception, feeling and behavior, and may occur alongside metamorphopsia [17]. Consequently, it has been suggested that schizophrenia may be a cause of AIWS [3]. The literature review by the authors of this article found only one case of a patient with AIWS who was diagnosed with schizoaffective disorder [13]. Potential explanations for this relative lack of evidence may include either the under-reporting of AIWS symptoms in patients with psychosis (e.g., because of disorganized behaviors or thoughts) or the tendency for psychiatrists to treat AIWS symptoms as symptoms of schizophrenia.

Although it may be difficult to differentiate AIWS from psychosis, compared with coenesthesias of psychosis, AIWS is usually characterized by intact insight, short-lived symptoms and an identified neurological etiology.

■ Toxic & pharmacological etiologies

Illicit drugs, such as lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine ('ecstasy'), mescaline and inhalants may produce hallucinations and metamorphopsia and unsurprisingly, have also been reported to induce phenomena such as AIWS. In a case report of a 15-year-old boy with no medical history who presented with acute symptoms of derealization, micropsia, macropsia and a sense of accelerated time over the course of 24 h, AIWS was attributed to cannabis use [8].

Takaoka *et al.* reported a case of toluene-based solvent abuse resulting in symptoms of AIWS [26]. After several years of abuse, the 22-year-old woman developed a distorted perception of her body, colors and time.

Much like illicit drugs, certain medications can induce visual hallucinations. To date, two cases of AIWS induced by the anticonvulsant topiramate have been published [27,28]. Evans and Rolak described a 31-year-old patient who developed AIWS 1 week after starting topiramate [29]. After 2 and a half months of intermittent AIWS episodes, topiramate was discontinued and the syndrome resolved gradually within 1 month. In the other case report, Jürgens *et al.* presented the case of a 17-year-old girl with a past history of migraine headaches without aura [27]. The patient complained of intermittent, nocturnal distortions of her body image, both macropsia and micropsia, with a dose above 75 mg/day. Approximately 2 weeks after topirimate was tapered off to 50 mg/day, the nocturnal phenomena ceased. Returning the dose to 75 mg/day again resulted in metamorphopsia.

Dextromethorphan, an NMDA antagonist, may also be involved in AIWS. The case of a 4-year-old girl developing AIWS (micropsia) within 36 h of administration of dextromethorphan, which remitted after drug discontinuation, was reported in the literature [8].

Finally, oseltamivir, a neuraminidase inhibitor prescribed in the treatment of flu symptoms has been reported to possibly induce neuropsychiatric symptoms, such as hallucinations [30]. In the two case reports of AIWS associated with the H1N1 infection [22,23], this drug was prescribed and its role in the onset of AIWS cannot be ruled out.

Potential pathophysiological pathways

The broader pathophysiology of AIWS is largely unknown and the multiple etiologies suggest many neurobiological mechanisms. Radiology (cranial computed tomography or MRI) has failed to demonstrate the involvement of any specific brain areas [31] and EEG data has only shown nonspecific electrophysiological abnormalities [3,17]. Results from a few neuroimaging studies, however, suggest the possible involvement of visual pathways [10,31–33]. Kuo *et al.* reported a hypoperfusion in the temporal lobe, occipital lobe and perisylvian area in four patients with AIWS using single-photon emission computed tomography brain scan [10]. The authors suggested that, independently from the etiology, AIWS may result from a focal brain parenchymal edema and a decrease in regional cerebral blood flow in the regions located close to the visual pathway and the associated visual cortex. Gencoglu *et al.* examined cerebral perfusion using single-photon emission computed tomography imaging in a 7-year-old girl presenting with AIWS occurring 15 days after an upper respiratory tract infection with tonsillitis and also found hypoperfusion near the visual pathway (in this case, in the right frontal and the right frontoparietal regions) [32]. Finally, a recent publication using functional MRI reported increased activation in both auditory and visual cortices in a patient with verbal auditory hallucinations and AIWS [13].

Another etiological pathway to AIWS may be a dysfunction in the NMDA neurotransmitter system. The pharmacological profile of topiramate includes the potentialization of GABA-A receptors and blockade of excitatory NMDA transmission; similarly, dextromethorphan has been shown to antagonize NMDA neurotransmission. The fact that both of these NMDA inhibitors may induce AIWS suggests that the syndrome's pathophysiological pathway may perhaps involve dysfunction in the NMDA neurotransmission system. NMDA inhibitors, such as ketamine, amantadine or memantine, have been known to induce hallucination, derealization and depersonalization similar to those associated with AIWS [31,34,35].

While there is minimal evidence on the pathophysiology of AIWS, more specific evidence exists on the pathophysiology of its distinct visual distortions. In a review of the neurophysiological and anatomical correlates of 'positive' visual pathologies, Ffytche *et al.* suggest that micropsia and macropsia are the result of mechanisms in the visual cortices failing to account for the extent of an object's retinal projection [36]. The authors propose that allesthesia, the transposition of objects in the visual field, may be due to disturbances in the integration of vestibular and visual inputs, possibly in the anterior parietal lobe [36].

Conclusion & future perspective

The AIWS is a clinical entity that has been described consistently over the past five decades in various cultural settings. While migraines headaches and epilepsy were the first and most frequent etiologies reported in the literature, a number of different infectious, neurological, toxic and psychiatric conditions have been found to possibly be accompanied by AIWS-like symptoms. To date, little is known regarding the specific pathophysiological pathways involved in this condition, but the available evidence points to the possible implication of the dysfunction of NMDA neurotransmission and/or inflammation and edema of cerebral regions close to the visual pathways.

In conclusion, it is probable that what is currently referred to as AIWS actually includes a number of very heterogeneous conditions. In the future, further research aiming to better define the criteria of this syndrome are warranted, particularly in view of the possible overlap with other rare syndromes that involve distortions in the perception of body parts such as Cotard's syndrome [25] or Koro syndrome (illusion of a shrinking penis) [37]. Future advances in the understanding of the neurobiology underlying 'positive' visual distortions will help inform whether or not AIWS should be considered a distinct condition.

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