Alice-in-Wonderland Syndrome in Patients with Migraine

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Authors’ contributions

This work was carried out in collaboration between all authors. Authors APR, GRT and JEA designed the study. Author JEA wrote the first draft of the manuscript. Authors JEA, AVS and KVS have been working with patients and analyzing clinical data. Authors JEA and EAK managed the literature searches and wrote final version of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Alice-in-Wonderland syndrome (AIFS) is a rare neuropsychological syndrome that includes paroxysmal distortion of the body schema, depersonalization, derealization, visual hallucinations, distorted sense of time, and deja vu and jamais vu experiences. Alice-in-Wonderland syndrome may be an equivalent of a migraine attack. The objective of this study was to evaluate the clinical particulars of Alice-in-Wonderland syndrome in patients suffering from migraine.

Place and Duration of Study: University Headache Clinic between June 2012 and November 2015.

Methodology: The study sample involved 14 subjects with migraine as defined in the

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ICHD-III-beta and AIWS (1 male and 13 females) with a mean age of 22.9±12.1 years. 13 patients had migraine with aura, and one subject had migraine without aura. All study subjects were somatically and psychiatric healthy. A specially designed and validated questionnaire was being used to assess symptoms in patients with AIWS.

**Results:** Alice-in-Wonderland syndrome was characteristically being developed in children and adolescents as part of a migraine aura, combined with a typical impairment of visual perception, or between attacks, and also had episodes of visual hallucinations. Older patients were characterized by only interictal, short (lasting a few seconds) phenomena, which was most commonly teleopsia.

**Conclusion:** The reported study indicates that Alice-in-Wonderland syndrome is a heterogeneous condition varying with different age subgroups among patients with migraine.

**Keywords:** Alice-in-Wonderland syndrome; migraine.

1. **INTRODUCTION**

“What a curious feeling!” said Alice; ‘I must be shutting up like a telescope.” ““Curiouser and curiouser!” cried Alice (she was so much surprised, that for the moment she quite forgot how to speak good English); ‘how I’m opening out like the largest telescope that ever was!”

Lewis Carroll, ‘Alice’s Adventures in Wonderland’.

In 1952, C. W. Lippman published a series of observations of unusual symptoms he had seen in patients suffering from migraine [1]. One of the patients described his experience this way: «I suddenly felt that I had become very tall. I was walking down the street, and it seemed like I could see the tops of the heads of the passers-by. I was very scared. This sensation felt real to such a degree that, having seen my reflection in a shop-front, I was extremely surprised to see my height was actually the same». Typical sensations of these patients were those of «a part of the body growing much larger», «time running way too fast», or «people around talking and moving too rapidly». C. W. Lippman also presumed that Lewis Carroll suffered from migraine with aura and thus credited his characters with some of his own experiences [1].

In 1955, J. Todd [2,3] also published a description of a series of cases (6 subjects) and formulated for the first time the clinical criteria of Alice-in-Wonderland syndrome (AIWS):

- Paroxysmal distortion of the body schema, micro- and macrosomatognosia;
- Depersonalization, derealization;
- Visual hallucinations;
- Distorted sense of time;
- Deja vu and jamais vu experiences.

Subsequent observations have demonstrated that the manifestations of AIWS vary considerably: from odour and taste distortion to complex, detailed perception disturbances [4,5,6,7,8]. Visual perception disturbances (in perceiving colors, shapes, and brightness) are the most frequent ones. L. Carroll clearly described the symptoms of macropsia (when objects appear larger) and micropsia (when objects appear smaller). «It did so indeed, and much sooner than she had expected: before she had drunk half the bottle, she found her head pressing against the ceiling, and had to stoop to save her neck from being broken». Our patients described their macropsia experiences like: «I went down to the underground station, and found that the walls of the station had become very very high. This was both charming and extremely frightening». Sometimes object sizes remain the same, but their shapes become altered (metamorphopsia). For instance, some part of a companion’s face becomes indistinct or blurred all of a sudden [6]. Patients with AIWS may also have other visual illusions: palinopsia or visual perseverations (a multiple repetition of a visual image), achromatopsia and chromatopsia (decreased and increased color brightness), pelopsia (when objects appear nearer and larger), teleopsia (when objects appear smaller and further away), autokinesis (perception of a stationary object as a moving one), the halo phenomenon (a “nimbus” around objects), positive or negative afterimage from moving objects, and the splitting phenomenon.

Visual and somatosensory illusions and hallucinations require that conditions such as occipital epilepsy, encephalitis, and psychosis should be excluded [9]. Besides, some symptoms of AIWS have been described in individuals taking some drugs, such as topiramate, antidepressants (trazodone, mirtazapine, maprotiline, nefazodone), neuroleptics (risperidone), dextromethorphan (an agent included in the formulation of some cough medicines), clomifene, interleukin-2, and narcotic
drugs (LSD, Ecstasy, marijuana, mescaline) [10,11]. Literature sources include a series of reports of AIWS developing in patients with infectious diseases (infectious mononucleosis (Epstein – Barr virus infection), influenza) [12,13,14,15].

Whether AIWS can be attributed to migraine or not is a matter of debate. On the one hand, this syndrome is an extremely rare condition [16]. In Liu AM, et al. [17] study among 48 patients with AIWS just 6% had migraine etiology. In Lanska J, et al. [18] study of 81 AIWS cases migraine was in 11%. On the other hand, some of the phenomena that have been described in AIWS sufferers are not rarely seen in migraine patients. A study by Morrison D. R. et al. revealed that 15 % of patients with migraine with an aura presented with perception disorders during most of their attacks and 4.3% of them had body schema abnormalities [19]. Ardila A, et al. [20] followed up a large group of patients (200) with migraine with aura and concluded that 20% of them had an aura accompanied by various neuropsychological and psychiatric disorders of which the most frequent were anomic aphasia (difficulty in recalling names of objects), difficulty in speaking, depersonalization, derealization, macropsia and micropsia, olfactory hallucinations, simultanagnosia, achromatopsia (absent color perception), chromatopsia (altered color perception), and palinopsia or visual perseverations.

AIWS is a rare and misdiagnosed syndrome. The objective of this study was to evaluate the prevalence and clinical particulars of AIWS in patients suffering from migraine.

2. PATIENTS AND METHODS

The study sample involved 14 subjects with migraine as defined in the third edition of the International Classification of Headache Disorders (ICHD-III-beta) [21] and AIWS (1 male and 13 females) with a mean age of 22.9±12.1 years. 13 patients had a migraine with an aura, and one subject had migraine without aura. All study subjects were somatically healthy. Neurologically, no abnormalities were observed in between attacks. All patients had no clinical diagnoses of epilepsy. The patients were examined by a psychiatrist who diagnosed no psychiatric disorders either. The following additional evaluations were carried out: complete blood count and blood chemistry, blood tests for antibodies to infections including Epstein – Barr virus, urinalysis, electroencephalography, MRI, and MR-angiography – no abnormalities were detected. A specially designed and validated questionnaire was being used to assess symptoms in patients with AIWS. All the patients were applied to University Headache Clinic, Moscow (tertiary center) in 2012-2015 years and gave informed consent. The reason of admission to University Headache Clinic was migraine headache. The study concept was a simple observational (case series).

Descriptive statistics were used to describe clinical data. The standard deviation, median and interquartile range, and proportions were calculated for normally distributed data, nonparametric data, and nominal data, respectively. For comparison in two groups Mann–Whitney U-test was used; p-value less than 0.05 was considered to indicate a statistically significant difference.

3. RESULTS

The prevalence of AWLS patients among the sample of University Headache Clinic was equal to 0.75%. Before the examination in University Headache Clinic, the diagnosis was incorrect in all 14 patients. 3 patients were hyperdignosed with stroke; 5 patients - with unspecified psychiatric disorder, 6 patients - with epilepsy. No patients were recruited by a general practitioner or a neurologist, patients came to the Headache Clinic on their own initiative.

The mean age of migraine onset was found to be 10.4±4.1 years, while AIWS had become manifest at a mean of 11.9±4.7 years. The onset of migraine had preceded the development of AIWS in all subjects. 12 subjects were diagnosed with an inherited migraine, and AIWS was found to be hereditary as well in 3 of them. The frequency of migraine attacks varied from 6 times per month to 1 in a year (1.6±1.5 a month), and that of AIWS episodes ranged from 4 times per month to 1 in a year (1.4±1.6 a month). No temporal correlation was identified between the occurrence of migraine attacks and that of the AIWS episodes. The symptoms of AIWS observed in the study subjects are summarized in Table 1. Table 1 shows that obligatory disturbances in patients with AIWS included distortion of the body schema, i. e. impaired perception of one’s own body or its parts, derealization, déjà vu, abnormal perception of passing time, and visual illusions, primarily macropsia, which corresponded to the classical descriptions of the syndrome given by C. W. Lippman and J. Todd [7].
Table 1. Symptoms of Alice-in-Wonderland syndrome in study subjects

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<td>Own body seen ‘laterally’ and ‘through objects’</td>
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*Some symptoms definitions: Derealization - perception of the external world so that it seems unreal; depersonalization - an anomaly of self-awareness; parasomnias - abnormal behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep; déjà vu - sensation that an event or experience currently being experienced, has already been experienced in the past; macropsia - visual perception, in which objects of the visual field appear larger than normal; micropsia - visual perception, in which objects of the visual field appear smaller than normal; pelopsia - visual perception, in which objects of the visual field appear nearer than normal; teleopsia - visual perception, in which objects of the visual field appear further than normal; chromatopsia - objects appear unnaturally colored and colorless objects appear tinged with color; achromatopsia - partial or total absence of color vision; positive afterimage - image continuing to appear in one's visual field after the exposure to the original image has ceased; palinopsia - persistent or recurrence of a visual image after the stimulus has been removed; autokinesis - a light can appear to move when stared at in the dark; dysmetropsia - distorted perception of image size; metamorphopsia - objects are seen as distorted in shape*
After enrollment patients were split into two groups. Two groups of patients with AIWS were recruited for the purpose of the reported study. The first group (8 subjects) consisted of children and adolescents (mean age, 13.9±2.2 years), while the second group (6 individuals) included older patients (mean age, 34.8±4.7 years). The first group was characterized by a statistically earlier age at migraine onset, comparing with the second group (7.2±3.1 years vs 11.9±3.2 years), (p=0.02), as well as by earlier development of AIWS (9.1±2.4 years vs 14.2±4.6 years), (p=0.01). First group of patients characteristically developed AIWS as part of a migraine aura in combination with the visual and sensory disorders typical for the aura, and they also had it between migraine attacks. The abnormal episodes lasted in this group for approximately 5 minutes. This pattern was observed in all 8 patients in the first group and in 3 patients in the second group. Five patients of the older group typically developed AIWS episodes between migraine attacks, their experiences were short (a few seconds) and mostly consisted of teleopsia, which was only observed in two patients in the younger group.

Besides, patients in the younger group were more prone interictal visual hallucinations (7 subjects in the younger group and 3 subjects in the older one). Patients of both age groups experienced paroxysmal, stereotypical visual hallucinations. Children saw characters from cartoons, fairy-tales, and movies, which were clearly distinct in space and extremely brightly colored, and moved from one place to another or ‘dissolved’. Adults perceived complicated geometrical figures and ‘splitting of the space’. Two patients saw themselves or a part of their body as if was from outside while hallucinating. Both these experiences were stereotypical, short-lived, and described as ‘seeing self and what was going on around as if from above, the room’s height, or as if laterally’. The duration of hallucination episodes was approximately 5 minutes. All patients remained critical about their hallucinations.

EEG obtained in the waking state demonstrated mild diffuse changes in bioelectrical activity and signs of midbrain dysfunction in all study subjects. In 13 out of 14 cases, EEG was recorded in between attacks. One recording was obtained during a teleopsia and macrosomatognosia episode. It revealed moderate diffuse changes in bioelectrical brain activity indicating an involvement of the occipital, parietal, and posterior temporal regions, predominantly on the left (against a background of hyperventilation, the occipital, parietal, and posterior temporal regions produced bilateral synchronous spike-waves and polyphasic discharges in the alpha and theta ranges with an amplitude varying from 1 to 275 µV, more pronounced on the left), as well as signs of midbrain dysfunction and hyperexcitability.

Study subjects did not receive any therapy for AIWS. Four patients with frequent migraine attacks were administered standard prophylactic treatment with topiramate or amitriptyline. One female patient developed abnormal taste perception while on topiramate therapy, and was subsequently switched to amitriptyline. The patients were followed up afterwards (the follow-up period lasting from 2 months to 8 years). Paroxysms persisted in four out of five patients who were followed up for longer than one year. These three patients showed a tendency towards less frequent episodes of AIWS. Occurrence of migraine attacks decreased in all patients with frequent attacks who were given prophylactic treatment.

4. DISCUSSION

The reported clinical study is one of the largest trials of Alice-in-Wonderland syndrome. A study by Ho C. S. et al., which had also enrolled 10 patients, demonstrated a favorable prognosis for AIWS, as paroxysms regressed spontaneously and did not necessitate treatment [22]. Weidenfeld A et al. [23] followed up 9 patients with AIWS and reported a favorable prognosis for the disease as well, as only two of their patients continued to experience their symptoms one year after the onset of the disease. Previous longitudinal studies and our own observations included not a single AIWS sufferer who would proceed to have a psychiatric disorder [22,23]. A trial reported by Weidenfeld A et al. [23], similarly to our study, revealed a hereditary predisposition to migraine and familial cases of AIWS, though without any clinical specifics. The phenomenology of AIWS described by Weidenfeld A et al. corresponded to the results of our study, with obligatory symptoms as well including distorted body schema and visual illusions (micropsia and macropsia).

Lanska J, et al. [18] analyzed 81 case reports and case series of AIWS identified by PubMed since 1955 and identified three types of AIWS syndrome: somesthetic, more typical for adult patients; visual, more typical for children, and...
mixed type. In our study 5 patients had visual type of AIWS and 6 patients had somesthetic type. In patients with visual type had earlier onset both of migraine and AIWS, AIWS symptoms were part of migraine aura and were lasting for minutes. In patients with somesthetic type of AIWS symptoms were being observed between migraine attacks and were lasting for seconds.

In our study, reports of visual hallucinations during waking time were provided by 10 patients and corresponded to the descriptions of asthenopic scotoma. Typical images they saw were those of people or animals ‘flowing’ from side to side or shaping from air flows and then ‘dissolving’. This phenomenon is termed as asthenopic scotoma. The Cheshire Cat is an example of asthenopic scotoma. «’All right,’ said the Cat; and this time it vanished quite slowly, beginning with the end of the tail, and ending with the grin, which remained some time after the rest of it had gone». «... She noticed a curious appearance in the air: it puzzled her very much at first, but, after watching it a minute or two, she made it out to be a grin ... In another minute the whole head appeared».

Detailed description of different types of hallucinations and illusions was performed in Smith R.A. et al. [24] study of 9 patients with migraine and AIWS. Similar to our study AIWL patients experience was variable and included auditory hallucinations and fear as well. A female AIWS patient of ours provided the following description of her hallucinations: «We were sitting picnicking, and suddenly the smoke of the fire started whirling fancifully and forming faces». «I was sitting in the kitchen, and I saw a moon coming out sideways from somewhere, and it had a face of someone I thought I knew. It teetered across the entire kitchen and disappeared in the corridor » (Picture 1).

Two patients among our study sample saw an image of their own body when hallucinating. This experience is called autoscopic hallucination [25]. Autoscopic hallucinations were first described by Carl Linnaeus, a Swedish naturalist who suffered from migraine and saw his own image moving beside him during the transitional period to an attack [26]. The development of autoscopic hallucination is believed to be associated with affection of the temporoparietal junction region [27].

The absence of considerable EEG changes in our study subjects, including times of AIWS paroxysms, implies a non-epileptic nature of this condition. The analysis of results obtained in previous studies that employed functional MRI, PET, EEG, and visual evoked potentials demonstrated changes resembling a typical migraine pattern. There have been reports of comorbidities combining AIWS and Miller Fisher syndrome (a variant of a typical migraine aura without headache) or AIWS and abdominal migraine; all of these disorders are presumed to be equivalent to migraine [28]. A paroxysm of AIWS, as well as a migraine aura, may be relieved by transcranial magnetic stimulation [29].

![Picture 1. AIWS patient’s hallucination drawing](image-url)

The progressive nature and the course of the disease constitute an important clinical characteristic of AIWS, which makes it resemble a migraine aura. She (Alice) said: «'Dear, dear! How queer everything is to-day! And yesterday things went on just as usual. I wonder if I've been changed in the night? Let me think: was I the same when I got up this morning? I almost think I can remember feeling a little different. But if I'm not the same, the next question is, Who in the world am I? Ah, THAT'S the great puzzle!...'». Lewis Carroll thus gives a description of depersonalization. «... 'I'll try if I know all the things I used to know. Let me see: four times five is twelve, and four times six is thirteen, and four times seven is – oh dear! I shall never get to twenty at that rate!'». After depersonalization, Alice develops acalculia. «... ‘Let’s try Geography. London is the capital of Paris, and Paris is the capital of Rome, and Rome – no, THAT’S all wrong, I'm certain!’». And amnesia. «... ‘I'll try and say “How doth the little —” and she crossed her hands on her lap as if she were..."
saying lessons, and began to repeat it, but her voice sounded hoarse and strange, and the words did not come the same as they used to do: —». Alice then has sensory aphasia. «As she said this she looked down at her hands, and was surprised to see that she had put on one of the Rabbit's little white kid gloves while she was talking. "How CAN I have done that?" she thought. 'I must be growing small again.'». After that, Alice also experiences microsomatognosia. If we try to identify the brain sites responsible for the abnormalities experienced by Alice, we will come to a conclusion of a gradual involvement of the temporal lobe, as evidenced by depersonalization (amygdala of the temporal lobe) — acalculia (posterior portion of the left angular gyrus) - amnesia (hippocampus) - sensory aphasia (posterior superior regions of the superior temporal gyrus), and finally microsomatognosia.

Based on the possible clinical variants, one can presume that AIWS is associated with dysfunction and impairment of neuronal links between the temporal, parietal, and occipital lobes. Kuo Y. T. et al. [13] carried out single-photon emission computed tomography (SPECT) studies in four symptomatic AIWS patients and detected decreased cerebral perfusion in the temporal and occipital lobe areas.

A number of completed electrophysiological and neuroimaging studies have revealed in AIWS a pattern of changes similar to those observed in migraine [30]. In particular, a study by Lahat E et al. [14] investigated visual evoked potential in 5 children with AIWS. A significant increase was demonstrated in P100-N145 amplitude compared with healthy control children. This amplitude returned to normal in a few weeks, after the syndrome had regressed. The authors mentioned that they had seen a similar pattern in migraine patients. Discussing the study results reported by the Lahat E, et al. [14], they hypothesized that AIWS is underlain by a transient, focal reduction in cerebral perfusion that is similar to the process of cortical spreading depolarization (CSD) observed during a migraine aura.

Brumm K, et al. [31] performed functional MRI during a micropsia episode in a boy with AIWS. The study included a passive test (with the patient being asked to look at a chess pattern) and active one (where Ponzo optical illusion-based tasks were given). The passive test results included less activation in the calcarine gyrus of the left cerebral hemisphere, comparing with other left-side and right-side regions, as well as with a control (a healthy child). The active test conducted in this child with the syndrome produced even more pronounced hypoactivation in the calcarine and lingual gyri on both sides, as well as hyperactivation in the upper portion of the postcentral gyrus in the left hemisphere and in the lower portion of the postcentral gyrus on both sides, comparing with the healthy child. The authors interpreted the obtained data as an inadequate response to the visual stimulus, particularly during the active test, as a result of occipital and parietal cerebral dysfunction.

AIWS can develop in non-migraineurs, against a background of infectious diseases associated with fever [12,13,14,15]. The fever can lead to lowering of the cortical neuron excitation threshold [32,33] and act as a possible trigger of the syndrome's manifestation. It should be mentioned that fever is a typical trigger for diseases associated with cerebral brain hyperactivation: epilepsy and familial hemiplegic migraine [34].

Therefore, AIWS and typical migraine aura may have the same neurobiological mechanism, i.e. increased sensitivity of the cerebral cortex (hyperexcitability) to exogenous and endogenous triggers. Cortical neuron hyperexcitability observed in AIWS may be the basis of a phenomenon similar to CSD that involves the occipital, temporal, and parietal lobes and explains the clinical manifestations.

Based on comparisons between previously obtained data and the results of our study, AIWS may be a heterogeneous condition, as this syndrome can both develop as part of a migraine aura and be an exclusively interictal event and can also vary in duration, from a few seconds to a few minutes. Clinical patterns of AIWS correlate with the patient's age: they are significantly more dramatic in children and adolescents, being accompanied by a considerable number of visual experiences. One possible explanation is the following. Normally, visual perception uses two pathways, a dorsal (occipital-parietal) and a ventral (occipital-temporal) one [35]. The dorsal pathway participates in the arrangement of actions requiring spatial visual control (movement of an object and its location in space), whereas the ventral pathway is responsible for recognition of the object (color, shape, size) [36]. Children have been shown to have immature neuronal inhibition mechanisms and a physiologically deficient
ventral pathway of visual perception [37]. This fact can explain the high occurrence of visual phenomena, in particular hallucinations, in children suffering from AIWS. Additionally, the immaturity of the ventral pathway of visual perception, along with the inhibition deficiency, may be the cause of the involvement of this region occurring with CSD during a migraine aura associated with AIWS. With advancing age, as the ventral pathway of visual perception matures and cortical excitability decreases, AIWS may regress or be manifested by short-lived ‘flashback’ events.

The pathogenesis of AIWS is not well known. The gradual spread and regression, development during a migraine attack and duration of symptoms AIWS confirms the common pathophysiological basis between migraine aura and AIWS. The symptom of aura in migraine is likely caused by cortical spreading depression. The symptoms of AIWS can be explained by focal cortical processes, oligemia, or depolarization. On the other hand, Alice in Wonderland syndrome has been attributed to migrainous cortical dysfunction in the nondominant posterior parietal lobule [38].

Our study has some limitations: a small number of patients, lack of data on the natural course of the disease. As AWLS is a rare and misdiagnosed syndrome, several study groups should provide a study with accordance to a single protocol.

5. CONCLUSION

AIWS is a heterogeneous condition with clinical patterns varying between different age subgroups with pathogenetic mechanisms that are also seen in migraine. Apart from the clinical evidence of the correlation between this syndrome and migraine, there is a pathophysiological basis for that as well. Similarly to migraine auras, AIWS appears to result from cortical hyperexcitability, which forms the basis for a phenomenon resembling cortical spreading depolarization, whereas the age-dependent visual patterns are due to the physiological specifics in the maturation of the visual perception pathways.

CONSENT

This research used de-identified administrative data obtained from University Headache Clinic; informed consent was not required.

ETHICAL APPROVAL

The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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