Down the rabbit hole: A case report of adolescent migraine heralding Alice in Wonderland syndrome

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Introduction: Alice in Wonderland syndrome (AIWS) is an uncommon perceptual disorder characterized by distortions of body image, visual perception and time. Although its association with migraine, particularly migraine with aura, is well recognized, AIWS remains absent from the International Classification of Headache Disorders, 3rd edition, the International Classification of Diseases, 10th revision and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, complicating its recognition. Overlapping genetic and psychiatric comorbidities – including depression with psychotic features – may further obscure the diagnosis. **Case presentation**: We describe an 18-year-old female with a 5-year history of continuous, side-alternating 'heavy and floating' headaches that intensified after menarche. Her course featured fluctuating sensory, motor, behavioral, cognitive, emotional and visual disturbances, including metamorphopsia, prosopometamorphopsia and time distortion. Brain magnetic resonance imaging, electroencephalography, cerebrospinal fluid analysis and autoimmune and infectious panels were largely unremarkable, whereas whole-genome sequencing identified a chromosome 16p11.2 duplication. Diagnoses of migraine with aura, AIWS and severe depressive disorder with psychotic features were established, and care was coordinated by a multidisciplinary team including specialists in neurology, pediatrics and psychiatry. **Conclusion**: Migraine with aura may serve as an early clinical clue to AIWS, particularly when accompanied by psychotic depression and an underlying chromosomal abnormality. Recognizing this overlap – and specifically distinguishing AIWS phenomena from mood-congruent psychotic hallucinations – enables timely multidisciplinary management.

Keywords

Adolescent, Alice in Wonderland syndrome, case reports, chromosome 16p11.2 duplication, cortical spreading depression, depressive disorder (major), DNA copy number variations, migraine with aura, perceptual disorders, psychotic depression

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Article Highlights

- Alice in Wonderland syndrome (AIWS) is a rare perceptual disorder that is not formally classified in the International Classification of Headache Disorders, 3rd edition, the International Classification of Diseases, 10th revision or the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, making clinical recognition dependent on careful history-taking.
- Migraine, particularly migraine with aura, may act as a clinical 'alarm' that heralds AIWS through the shared mechanism of cortical spreading depression.
- In the systematic review by Blom, published AIWS cases fall into three principal clusters: predominantly somesthetic (Type A), predominantly visual (Type B) and mixed visual–somesthetic (Type C), with migraine, encephalitis, epilepsy and head trauma as the main etiologies. Our patient fits Type C, with associated time and self-perception disturbances.
- An 18-year-old female presented with refractory migraine with aura, multimodal perceptual disturbances and severe depressive disorder with psychotic features.
- Psychotic depression can produce mood-congruent auditory and visual hallucinations that mimic or coexist with AIWS phenomena, so disentangling the two is essential before attributing all perceptual symptoms to migrainous aura.
- Whole-genome sequencing identified a chromosome 16p11.2 duplication, a copy-number variant implicated in a wide range of neurodevelopmental and psychiatric conditions, including psychosis.
- A multidisciplinary approach involving neurology, pediatrics and psychiatry is essential when migraine, AIWS, psychotic depression and genetic susceptibility co-occur.

Alice in Wonderland syndrome (AIWS) is an uncommon perceptual disorder characterized by distortions of body image and visual perception, including micropsia, macropsia, pelopsia and teleopsia. The syndrome was first delineated by Todd on the basis of Lewis Carroll's literary depictions and is now recognized as a heterogeneous entity with multiple etiologies.[1–3] Its pathophysiology is closely linked to cortical spreading depression (CSD), a self-propagating wave of neuronal and glial depolarization that plays a well-established role in migraine aura. In addition, migraine, particularly migraine with aura, can act as an early clinical marker or 'alarm' for the presence of AIWS because of this shared mechanism.[1–3]

Despite growing awareness, AIWS is not included in the International Classification of Headache Disorders, 3rd edition (ICHD-3), the International Classification of Diseases, 10th revision (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and its overlap with migraine aura, psychiatric disturbances and genetic syndromes creates substantial diagnostic uncertainty. Chromosome 16p11.2 duplication, a recurrent copy-number variant associated with neurodevelopmental and psychiatric conditions, may further modulate the phenotype in susceptible individuals. This case is unique in illustrating how persistent migraine with aura served as a clinical alarm for AIWS in an adolescent with chromosome 16p11.2 duplication and comorbid severe depressive disorder with psychotic features, thereby contributing to the emerging literature on migraine as both a trigger and a diagnostic marker of this rare syndrome.

Case report

Patient information and clinical presentation

An 18-year-old female presented to the Department of Neurology, Dr. Cipto Mangunkusumo National General Hospital, with a 5-year history of 'heavy and floating' headaches that had worsened 1 week before admission. The headache first appeared at age 13, preceded by fever, and was strictly lateralized but alternated between the right and left hemicranium. At onset, episodes lasted 2–5 h and recurred 5–6 times per day but over time evolved into continuous, daily pain. Attacks were frequently preceded by an ascending aching sensation that extended from the soles of the feet to the upper extremities and head over a period of 2 h to 1 day. Frequency and duration intensified after menarche at age 14. Baseline pain intensity was a Numeric Rating Scale (NRS) score of 3, with intermittent exacerbations to NRS scores of 7–8 occurring 1–2 times per day.

Associated manifestations were grouped into six domains. Sensory: recurrent ascending limb pain culminating in headache, accompanied by visual distortion and reduced movement. Motor: sudden falls to the right, right-sided weakness and the sensation that her foot was not touching the ground. Behavioral: episodes of age-inappropriate behavioral shifts lasting 10–30 min, during which her language, affect and mannerisms transiently resembled those of either a markedly younger child – showing dependency behaviors expected of a 3- or 5-year-old – or an individual in her 30s, with a formal register and age-advanced behaviors. Both states were qualitatively distinct from her baseline presentation at age 18 and were consistently witnessed by family members, although regressive, child-like symptoms were more predominant. Cognitive: disorganized speech with fantastical content, such as wanting to ride a *Tyrannosaurus rex*, being in outer space or diving in the sea. She responded affirmatively despite the incoherence of the content. Emotional: outbursts of anger followed by hiding, a wide-open, unresponsive gaze and screaming, lasting up to 1 h. Visual: perception of a person whose head transformed into an animal and of puzzle-like patterns on the wall, together with recurrent auditory and visual hallucinations occurring with or without headache.

Past medical history included suspected limb–girdle muscular dystrophy and porphyria, both subsequently ruled out. Family history was notable for a younger sibling with primary immunodeficiency; consanguinity was denied. The patient was born at term following resuscitation, with appropriate growth and development apart from delayed speech. From a psychosocial perspective, she had been homeschooled since senior high school, with rigid social patterns and maternal overprotectiveness.

Ethics statement

This manuscript describes a retrospective case report based on secondary data obtained from existing medical records, without any prospective intervention or additional procedures. All patient-related information has been anonymized to ensure confidentiality and prevent identification of the patient. An informed consent from the patient has been obtained.

Diagnostic assessment

Neurological examination was unremarkable. Neurodevelopmental assessment yielded an Autism Spectrum Quotient (ASQ) score of 24, indicating autistic traits with impaired attention switching (reduced flexibility) and heightened attention to detail. On the Adolescent/Adult Sensory Profile (AASP), the patient demonstrated high sensory sensitivity, frequently modifying her environment to avoid overload; sensory overstimulation triggered meltdowns or shutdowns. Brain magnetic resonance imaging (MRI) revealed left frontal demyelination, bilateral hippocampal sclerosis spectrum and right hippocampal inflammation. Cerebrospinal fluid analysis, meningitis and autoimmune encephalitis panels, autoimmune screening, electromyography and electroencephalography (EEG) were all within normal limits. Whole-genome sequencing performed 1 year earlier identified a chromosome 16p11.2 duplication.

Table 1: Summary timeline of clinical events, investigations and management

Age/time point	Clinical event/intervention
Birth	Term delivery after resuscitation; appropriate growth; delayed speech development
Age 13 (5 years before admission)	First episode of 'heavy and floating' headache preceded by fever; unilateral, alternating; 2–5 h per episode, 5–6 times/day
Age 14 (menarche)	Marked worsening in frequency and duration; progression toward continuous daily headache; NRS 3 baseline with NRS 7–8 exacerbations
Preceding years	Recurrent multimodal disturbances (sensory, motor, behavioral, cognitive, emotional and visual) with auditory and visual hallucinations
Prior evaluations	Meningitis and autoimmune encephalitis panels, autoimmune screening, electromyography and EEG – all within normal limits. Limb–girdle muscular dystrophy and porphyria excluded
1 year before admission	Whole-genome sequencing under pediatric care revealed a chromosome 16p11.2 duplication
1 week before admission	Worsening refractory migraine-type headache with intensified aura features and perceptual disturbances
Admission (age 18)	Brain MRI: left frontal demyelination, bilateral hippocampal sclerosis spectrum and right hippocampal inflammation. ASQ score of 24; AASP: high sensory sensitivity. Diagnoses established: migraine with aura + AIWS, chromosome 16p11.2 duplication and severe depressive disorder with psychotic features
On-going care	Multidisciplinary management (neurology, pediatrics and psychiatry) with preventive migraine therapy, antidepressant and antipsychotic optimization and psychosocial support; adherence good; no adverse events; symptoms persistent but stable

AASP = Adolescent/Adult Sensory Profile; AIWS = Alice in Wonderland syndrome; ASQ = Autism Spectrum Quotient; EEG = electroencephalography; MRI = magnetic resonance imaging; NRS = Numeric Rating Scale.

Based on the clinical history and ancillary examinations, the patient fulfilled the ICHD-3 criteria for migraine with aura, including visual, sensory, speech, motor and brainstem symptoms, with gradual spread of at least one aura symptom over ≥5 min, two or more aura symptoms occurring in succession, each individual aura lasting 5–60 min, at least one positive aura symptom and headache within 60 min of the aura. Red-flag features – atypical aura, fever, focal neurological deficit, memory impairment, altered consciousness and personality change – were carefully excluded. A working diagnosis of AIWS was made in view of episodic, fluctuating perceptual distortions temporally and clinically associated with migraine. Additional diagnoses included severe depressive disorder with psychotic features and chromosome 16p11.2 duplication.

Therapeutic intervention and follow-up

Care was coordinated by a multidisciplinary team involving neurology, pediatrics and psychiatry. No disease-specific therapy is available for AIWS or chromosome 16p11.2 duplication; therefore, management focused on preventive migraine therapy, psychiatric stabilization (including antidepressant and antipsychotic optimization under psychiatric supervision) and psychosocial support. The patient adhered to the multidisciplinary management plan without tolerability issues, and no adverse or unanticipated events were observed. At follow-up, symptoms remained persistent but stable, with fluctuating headache intensity; the patient and her family acknowledged the burden of recurrent symptoms but expressed cautious relief regarding the current diagnosis and coordinated care, emphasizing the importance of on-going support to maintain daily function and quality of life. A summary timeline of clinical events is provided in *Table 1*.

Discussion

Migraine headache as an alarm

The patient first developed a headache at age 13, described as a 'heavy and floating' pain alternating between the right and left sides of the head, with progressive worsening after menarche at age 14. Recurrent moderate-to-severe headaches accompanied by visual aura and symptom onset around puberty pointed to migraine as the initial impression. She fulfilled the ICHD-3 criteria for migraine with aura, with visual, sensory, speech, motor and brainstem features and four of the required aura characteristics. Red-flag conditions were carefully excluded.[4,5]

Migraine typically evolves through four phases. The premonitory phase, arising hours to days before headache onset, features nonaura symptoms such as fatigue, irritability, mood change, concentration difficulty, nausea, blurred vision, photophobia, phonophobia and neck stiffness; neuroimaging implicates hypothalamic dysfunction, with dopamine and orexin signaling as key drivers. The aura phase affects up to one-third of patients, most often with visual disturbance but also sensory, language, motor, brainstem and retinal symptoms, and is thought to reflect CSD. The headache phase arises from complex interactions between peripheral trigeminal afferents and central pain-processing networks, with calcitonin gene-related peptide playing a central role; chronic migraine may develop through impaired descending pain modulation and progressive sensitization. The postdrome phase follows headache resolution and is characterized by neuropsychiatric, sensory and gastrointestinal symptoms lasting about a day. Functional imaging suggests overlapping neural mechanisms between the premonitory and postdrome phases, underscoring the need for rest, lifestyle adjustment and preventive strategies in comprehensive migraine management.[4,5]

In this patient, clinical manifestations were mapped to the migraine phases. Premonitory symptoms included anger and emotional outbursts, behavioral regression, urinary frequency and fatigue. Aura symptoms comprised visual distortion, disorganized speech with fantastical content, ascending limb aching and sudden weakness. The persistence and evolution of these symptoms over several years, coupled with their close temporal relationship to headache, supported the interpretation of migraine as a clinical alarm for the underlying AIWS.

Alice in Wonderland syndrome

The diagnostic approach to suspected AIWS began with the presence of episodic, fluctuating visual disturbances that were temporally and clinically associated with migraine. Although brain MRI revealed left frontal demyelination, bilateral hippocampal sclerosis spectrum and right hippocampal inflammation, no AIWS-specific structural lesion was identified; EEG, cerebrospinal fluid analysis and autoimmune panels were within normal limits, thereby supporting the consideration of migraine aura and/or AIWS as the primary mechanism underlying the perceptual disturbances.

AIWS is associated with structural and functional abnormalities of the perceptual system, most often arising from central nervous system pathology, although similar distortions can result from retinal or labyrinthine disease. Cortical regions such as visual area V4 (associated with color processing) and visual area V5, also known as the middle temporal area (associated with motion processing), together with orientation columns of the visual cortex, are implicated in distortions such as achromatopsia, akinetopsia, plagiopsia and metamorphopsia. These disturbances reflect dysfunction of specialized neuronal populations or mismatches within broader visual networks, as illustrated by prosopometamorphopsia; imaging studies link micropsia to occipital hypoactivation and parietal hyperactivation.

The systematic review by Blom cataloged the published literature on AIWS and organized its phenomenology into three principal symptom clusters.[2] Type A denotes cases in which somesthetic distortions predominate – most notably microsomatognosia and macrosomatognosia, in which parts of the body or the body as a whole are perceived as smaller or larger than their actual size. Type B denotes cases in which visual distortions predominate – micropsia, macropsia, pelopsia, teleopsia, dysmetropsia and metamorphopsia (including prosopometamorphopsia). Type C denotes cases in which both visual and somesthetic distortions coexist. Related phenomena documented across these clusters include altered perception of time, derealization and depersonalization, akinetopsia, auditory distortions and multimodal illusory experiences. In Blom's cohort, encephalitic and other infective etiologies accounted for the largest proportion of cases, followed by migraine, epilepsy, head trauma, drug effects and a residual idiopathic group.[2] Mapped onto this framework, our patient's phenomenology – visual distortions (prosopometamorphopsia, puzzle-like patterning on walls and fantastical visual imagery), somesthetic alterations (altered perception of limb position and movement, the sensation that her foot was not touching the ground and ascending aching sensations), time distortion and depersonalization-like dissociation – most closely fits Type C, with associated time and self-perception disturbances, within a migraine-related etiological category.

However, as AIWS is not recognized in major classifications such as ICD-10 or DSM-5, diagnosis relies on careful history-taking, thorough neurological and physical examinations and familiarity with its varied presentations. When central causes are suspected, EEG, MRI and blood studies may be performed, although they are often normal. Differential diagnosis remains complex, requiring exclusion of hallucinations and illusions, determination of underlying causes and clarification of whether symptoms are causally linked to the identified disorder, since perceptual distortions can also occur in healthy individuals or as adverse effects of therapy. In relation to migraine aura, one study reported that AIWS occurs in approximately one in five patients with migraine, with prevalence doubling among those with migraine with aura, indicating that it is more common than generally assumed; its true frequency may be underestimated because of patient underreporting. Preventive migraine therapy has been shown to reduce or eliminate AIWS episodes, further supporting the role of CSD in its pathophysiology.[6,7]

Overlapping psychiatric manifestations

An ASQ score of 24 in this patient indicated autistic traits, such as impaired attention switching (reduced flexibility) and heightened attention to detail. These features corresponded to MRI findings of left frontal demyelination, bilateral hippocampal sclerosis and right hippocampal inflammation. Frontal demyelination disrupts cognitive flexibility, whereas frontal rigidity and hippocampal dysfunction reinforce detail-focused processing.

On the AASP, she demonstrated high sensory sensitivity, often modifying her environment to avoid overload; sensory overstimulation (noise, light, touch, pain and anxiety) triggered distress, expressed as meltdowns (outbursts and hyperactivity) or shutdowns (mutism, withdrawal and dissociation).[8] Right hippocampal inflammation and limbic hyperexcitability may underlie sensory sensitivity, whereas bilateral hippocampal sclerosis impairs memory–emotion integration, contributing to dissociation. Pain was linked to right hippocampal inflammation with central hyperalgesia.[9]

Migraine further exacerbated sensory hypersensitivity (photophobia, phonophobia and osmophobia) and intolerance, often precipitating meltdowns in autism.[8] Anxiety and frustration amplified pain perception, producing a cycle of pain, stress and emotional dysregulation, which is more pronounced in autism because of limited coping capacity.[8] The differential diagnosis of AIWS is complex, requiring distinction from hallucinations and illusions, exclusion of underlying conditions with similar symptoms and clarification of whether perceptual distortions are truly attributable to the diagnosed disorder, since such phenomena can also occur in the general population without pathological significance.[6,7] In this patient, dissociative features were observed, marked by impaired perception and misinterpretation of sensory experience. The chromosome 16p11.2 duplication is considered a precipitating factor, heightening pain perception and sensitivity compared with those in the general population and producing exaggerated responses. Both physical and emotional pain appeared to trigger dissociative episodes, which in this case may function as a coping mechanism.

A particularly important consideration in this patient is the formally established diagnosis of severe depressive disorder with psychotic features, which may contribute substantively to the perceptual, cognitive and emotional phenomena described rather than being a mere comorbidity.[10] Psychotic depression classically involves mood-congruent auditory and visual hallucinations, nihilistic or guilt-laden delusional thought content and marked psychomotor disturbance, and these phenomena can superficially mimic – or coexist with – AIWS-type perceptual distortions.[10] The recurrent auditory and visual hallucinations observed in our patient, including the perception of faces transforming into animals, puzzle-like wall patterns and fantastical imagery, may therefore have a dual origin: CSD and migrainous aura on the one hand and the psychotic process of her depressive illness on the other. Depressive episodes may also lower the threshold for central sensitization and amplify pain, hypersensitivity and dissociative responses, which can in turn precipitate the behavioral outbursts, withdrawal and age-shifted presentations that could otherwise be misattributed solely to AIWS or to the underlying 16p11.2 duplication. Notably, chromosome 16p11.2 duplication is itself associated with an elevated risk of psychotic illness, providing a biologically plausible link between genetic susceptibility, psychiatric comorbidity and the complex phenomenological picture seen here.[11,12] Disentangling the relative contributions of psychotic depression and AIWS is difficult in a single cross-sectional presentation; longitudinal observation, particularly of whether perceptual phenomena track with mood state (resolving as the depressive episode remits) or with migraine attacks (clustering around headache phases), will be essential, and antidepressant and antipsychotic optimization should be considered part of the diagnostic as well as the therapeutic strategy.

Chromosome 16p11.2 duplication

Under prior pediatric care, whole-genome sequencing revealed a chromosome 16p11.2 duplication. This genetic finding is considered relevant to the current symptoms and contributes to the complexity of her clinical presentation.

Chromosome 16p11.2 duplication is a recurrent copy-number variant involving a 600 kb segment on chromosome 16 that contains genes crucial for brain development. Although rare in the general population (0.07%), it is one of the most frequent genetic causes of autism spectrum disorder and is associated with a broad range of neurodevelopmental and psychiatric conditions, including developmental delay, intellectual disability, speech and language impairment, attention-deficit/hyperactivity disorder, anxiety, depression and psychosis. Neurological manifestations may include hypotonia, motor coordination difficulty, seizures, tremor and EEG or MRI abnormalities, whereas physical findings often involve microcephaly or macrocephaly, low body weight and occasional congenital anomalies. The condition shows incomplete penetrance and variable expressivity, with clinical outcomes ranging from asymptomatic carriers to severe impairment, influenced by duplication size, coexisting genetic variants and environmental factors. Diagnosis relies on genetic testing, such as array-comparative genomic hybridization, and management requires a multidisciplinary approach addressing developmental, psychiatric and neurological needs.[11,12]

Strengths and limitations

Strengths of this case include comprehensive longitudinal documentation of the clinical evolution, detailed categorization of symptoms according to migraine phases and Blom's AIWS phenomenological framework, and the integration of genetic findings through whole-genome sequencing, which added explanatory depth. Limitations include the absence of AIWS-specific abnormal findings on several ancillary tests (MRI and EEG), which limits definitive pathophysiological confirmation, and the lack of disease-specific treatment options, which makes long-term outcomes uncertain. As a single-patient report, generalizability is inherently limited and observer bias in linking perceptual and psychiatric phenomena to the genetic finding cannot be excluded. In addition, because the patient was in an active depressive episode with psychotic features at the time of assessment, we were unable to formally attribute each perceptual phenomenon to a single pathophysiological process (migrainous aura, AIWS or psychotic depression); longitudinal reevaluation across euthymic and depressed states will be required to clarify this.

Conclusion

This case illustrates the clinical complexity that arises from the interplay of migraine with aura, AIWS, psychotic depression and chromosome 16p11.2 duplication. The patient's symptoms span all migraine phases and overlap with perceptual, dissociative and psychotic disturbances, highlighting the diagnostic challenge of distinguishing AIWS from aura, mood-congruent psychotic hallucinations and primary psychiatric disorders. Mapping her phenomenology onto Blom's AIWS framework placed her within the mixed visual–somesthetic (Type C) cluster, with associated time and self-perception disturbances. The identification of chromosome 16p11.2 duplication as a contributing factor emphasizes the role of genetic susceptibility in modulating pain perception, neuropsychiatric symptoms and clinical heterogeneity. Thorough clinical evaluation, exclusion of red-flag conditions and integration of neurological, psychiatric and genetic perspectives remain essential in both diagnosis and management, and a multidisciplinary approach is critical to address the overlapping symptom domains and optimize care in patients with such complex presentations.

Patient perspective

The patient and her family acknowledged the substantial burden imposed by years of unremitting headaches and unpredictable perceptual, emotional and behavioral episodes. They described relief at having a coherent, unifying diagnosis after multiple prior evaluations and valued the coordinated involvement of neurology, pediatrics and psychiatry. They emphasized the importance of continued support to preserve daily function, schooling and quality of life and expressed willingness to share this experience to help raise awareness of AIWS in adolescents. ❑

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