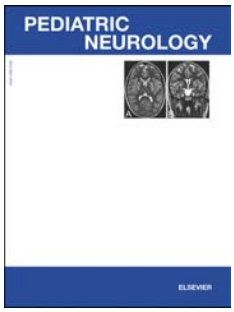
Accepted Manuscript



Alice in Wonderland Syndrome: Presenting and Follow-up Characteristics

Alessandra M. Liu, Jonathan G. Liu, Geraldine W. Liu, ALM Grant T. Liu, MD

PII: S0887-8994(14)00213-6

DOI: 10.1016/j.pediatrneurol.2014.04.007

Reference: PNU 8332

To appear in: *Pediatric Neurology*

Received Date: 22 December 2013

Revised Date: 31 March 2014

Accepted Date: 5 April 2014

Please cite this article as: Liu AM, Liu JG, Liu GW, Liu GT, Alice in Wonderland Syndrome: Presenting and Follow-up Characteristics, *Pediatric Neurology* (2014), doi: 10.1016/j.pediatrneurol.2014.04.007.

Alice in Wonderland Syndrome: Presenting and Follow-up Characteristics

Alessandra M. Liu; Jonathan G. Liu; Geraldine W. Liu, ALM; Grant T. Liu, MD

from the Neuro-ophthalmology Service of the Children's Hospital of Philadelphia and the Departments of Neurology and Ophthalmology, Perelman School of Medicine at the University of Pennsylvania.

Corresponding author: Dr. Liu, Division of Ophthalmology, Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, PA 19104. Phone (215)590-2791. Fax (215)590-4325. email: liug1@email.chop.edu.

Shorter Running Title: Alice in wonderland syndrome

Word Count: 1926

Abstract

Background: To investigate the distribution of symptoms and etiologies of patients with Alice in Wonderland syndrome (AWS) (visual perception of change in one's body size) and AW-like syndrome (AWLS) (extrapersonal illusions) at presentation and to determine their prognosis.

Design: Retrospective chart review and telephone interview.

Methods: Charts of children diagnosed with AWS by a pediatric neuro-ophthalmologist between July 1993 to July 2013 were reviewed. Patients seen prior to 2012, or their parents, were contacted for follow-up information.

Results: 48 patients (avg. age 8.1 years) diagnosed with AWS/AWLS were identified. Common visual symptoms were micropsia (69%), teleopsia (50%), macropsia (25%), metamorphopsia (15%), and pelopsia (10%). MRI and EEGs were unrevealing in 21/21 and 23/23 cases respectively. The etiology was infection in 33% and migraine and head trauma in 6% each. No cause was found in 52%. Of the 15 patients with follow-up, 20% had a few more events of AWS/AWLS which eventually stopped after initial diagnosis, 40% had no more events, and 40% were still having AWS/AWLS symptoms at the time of the interview, while 4 (27%) developed migraines and 1 (7%) seizures since the diagnosis.

Conclusion: AWS/AWLS typically affects young children, and the most common visual complaints are micropsia and teleopsia. The most common cause is infection, but half of cases have no obvious etiology. MRI and EEG are unhelpful. Usually symptoms of AWS/AWLS stop eventually, but in over one third of the

cases, they continue. One third of patients without a history of migraine may subsequently develop migraine.

Key words: Alice in wonderland syndrome, teleopsia, pelopsia

Introduction

Patients with the Alice in Wonderland syndrome (AWS) experience hallucinations or illusions of expansion, reduction, or distortion of body image.[1] The label comes from the classic story of *Alice's Adventures in Wonderland*, written by Lewis Carroll (Charles Lutwidge Dodgson) in 1865.[2] Lippman[3] first described AWS, then subsequently Todd[4] gave the condition its name.

Individuals with true AWS perceive their own body parts changing size. Lanska et al.[5] referred to this as "Type A" AWS. Micropsia (objects appear too small), macropsia (objects appear too large), metamorphopsia (objects appear too fat, thin, short, tall, etc.), teleopsia (objects appear further away than they are), and pelopsia (objects appear closer than they are)[1] are extrapersonal visual complaints similar to AWS. Lanska et al.[5] referred to them as "Type B". Lanska et al.[5] categorized "Type C" complaints as altered perception in ones body image and externally other people or objects as well. To distinguish self vs. extrapersonal illusions, for the purposes of this study we will term Type B and C as Alice in Wonderland-like syndromes (AWLS). Other authors[6] have also advocated this distinction.

The cause of AWS/AWLS is not known. Various authors however have attributed the condition to migraine, epilepsy, and infections. Lippman's seven cases experienced migraine headaches with altered perception in body image.[3] The migraines occurred before, during, or after the AWS symptoms.[3] In three of six of Todd's cases,[4] there was a family history of migraines and/or epilepsy. Golden's two cases with AWS had repeated headaches and a strong family

history of migraines.[6] In addition, Copperman[7] presented three cases with AWS as a presenting symptom of infectious mononucleosis.

The purpose of this paper is to investigate the distribution of symptoms and etiologies of AWS/AWLS at presentation. Aside from one large meta-analysis,[5] this information is not available for a large series, particularly a pediatric one. The secondary aim is to determine the prognosis of these patients, since most studies focused only on the presenting AWS/AWLS symptoms and neither followed these patients after the initial onset nor ascertained whether other neurological diseases developed.

Methods

Eligible study participants included children between one and eighteen years of age seen in a pediatric neuro-ophthalmology practice at the Children's Hospital of Philadelphia from July 1993 to July 2013 who were diagnosed with Alice in Wonderland Syndrome. These children were identified by searching a master list of pediatric patients seen by a single physician (GTL).

For the prospective portion of the study, in order to insure an adequate time for follow-up, only those patients seen prior to 2012 from the eligible list of patients above were considered. Telephone contact information for the patients, patients' parent(s) and/or guardian(s) was obtained from the medical record and used to contact the patient (if >18 years old), parent(s), and/or guardian(s). Informed consent for enrollment in the study was obtained from patients and their parents/guardians via telephone. Enrolled participants then answered a brief pre-

drafted telephone questionnaire. The patients (or parent of the patient) were asked if the AWS/AWLS symptoms persisted after the initial diagnosis, if there were new visual symptoms, if the patient was subsequently diagnosed with migraines and/or seizures, if there were any new major medical and/or neurological problems that developed, and if there had been additional testing after the initial diagnosis.

For the retrospective portion of the study, charts from the following groups of patients were reviewed: i) those who participated in the prospective portion of the study; ii) eligible study candidates who could not reached by telephone after three consecutive attempts or because their contact information was no longer valid - a waiver of consent was obtained from the Children's Hospital Institutional Review Board for their participation; and iii) patients seen in 2012 and 2013.

Charts for the retrospective portion of the study were reviewed for the following information: date of birth; date of initial visit; gender; relevant medical conditions; whether or not they experienced teleopsia, pelopsia, micropsia, macropsia, metamorphopsia, other illusions, or true AWS; history of migraines; family history of migraines; history of seizures; neuro-ophthalmic examination findings including refraction and dilated fundus examination; results of brain magnetic resonance imaging (MRI), brain computerized tomography (CT), or electroencephalography (EEG); etiology of the AWS/AWLS (migraine, seizure, infection, or other cause). Migraine was defined as headache with any of the following: classic visual aura, photophobia, phonophobia, nausea, or vomiting or abdominal migraine. A family history for migraine was considered positive if a

first-degree relative had migraine. Infections included streptococcus, flu-like illnesses (fever, malaise), gastrointestinal illnesses (nausea, vomiting), and upper respiratory illnesses.

The MRI or CT was considered unremarkable if normal or if only incidental abnormalities (cysts; small non-enhancing, non-periventricular white matter lesions; or venous anomalies, for instance) were found and no mass lesions, infarcts, or hemorrhages were found which may have caused a seizure or visual complaint. The neuro-ophthalmic examination was considered unremarkable if causes of visual distortion were ruled out by documentation of a normal anterior segment and fundus exam, and no or minimal astigmatism was found on cycloplegic refraction done at the time of the exam or by a referring pediatric ophthalmologist. In particular the maculae were examined carefully to rule out a retinal cause of metamorphopsia.

The cause of the AWS/AWLS was determined to be migraine when the individual's visual complaints occurred in association with a headache; seizure if the visual complaints had an EEG correlate on random or ambulatory monitoring; or infection if the visual complaint occurred within days of the illness.

This study was conducted in full accordance with all applicable Children's Hospital of Philadelphia research policies and procedures and all applicable federal and state laws and regulations including 45 CFR 46.

Results

Forty-eight patients between 1 and 18 years of age were diagnosed with Alice in Wonderland Syndrome between July 1993 to July 2013. Records were available for all 48 patients for the retrospective portion of the review. All patients had a normal neuro-ophthalmic examination without significant astigmatism or macular disease. Table 1 summarizes the patient demographics, visual and other symptoms, relevant medical and family histories, test results, and etiologies for these 48 patients.

Twenty-eight patients were seen prior to 2012 and were therefore eligible for the prospective portion of the study. Fifteen of the 28 (54%) patients and/or parents completed the telephone interview. Four individuals were contacted however did not choose to complete the phone interview but did not decline participation in the retrospective portion of the study. Nine patients could not be reached - three because the contact information was no longer valid and six because contact could not be made despite three attempts.

Of the 15 people who were interviewed, the interval between initial diagnosis and telephone contact was 2.1 to 13.53 years, with an average of 6.5 years (Table 2). Three (20%) had a few more events of AWS/AWLS after initial diagnosis, but these eventually stopped. Six (40%) had no more events. Six (40%) were still having AWS/AWLS symptoms at the time of the interview. Two of these six developed new visual symptoms: one patient mixed up numbers and saw figures and shapes that were not there; another patient viewed things as moving in a wave-like sort of motion and had a feeling of things moving. Four (27%) developed migraines after the initial diagnosis that did not have migraines

at the initial diagnosis. One (7%) had a seizure after the diagnosis. One (7%) was subsequently diagnosed with attention deficit disorder (ADD). Five (33%) parents of affected patients stated that they had experienced AWS/AWLS symptoms. Four of these parents stated they had had these symptoms since childhood. These four parents did not realize until after the initial visit and diagnosis of AWS/AWLS in their children that they also had had similar symptoms.

Discussion

The prospective portion of our study revealed the following: the prognosis for further AWS/AWLS episodes varies from individual to individual. For some patients there were no more episodes after diagnosis, and for others there were a few more episodes which eventually resolved. Several patients' symptoms, however, persisted and still occurred, sometimes in varied forms. After the initial diagnosis, the development of seizures was rare, but development of migraines was common. No other major medical, neurological, or psychiatric problems subsequently developed (only one person had ADD). Since there was a family history of AWS/AWLS in a portion of our patients, the cause of the condition may have had a genetic component in some cases.

The important findings from the retrospective part of the study are: most patients had teleopsia and micropsia. Very few had the true Alice in Wonderland syndrome. The majority of the patients are male. Almost half had a history of migraine in the family. Among patients tested, almost all had a normal MRI or

EEG. The most common identified cause was infection, but more than half the patients had no obvious cause.

Most of our results corroborate the findings of the meta-analysis of Lanska et al.[5] and the smaller series of Weidenfeld et al.[8] The average age of our patients is 8.1 years, and median is 7.9 years, which is very similar to the median age of Type B patients reported by Lanska et al. (7.5 years). Extrapersonal symptoms were most common in Lanska et al.'s study as well, with 75% of patients having Type B. Type A was uncommon (only 9%). Weidenfeld et al.'s patients were all generally in good health. In most of their cases, symptoms of AWS/AWLS ceased within several weeks of diagnosis (7/9, 78%). In our study, 60% of the patients' symptoms terminated before or subsequently after diagnosis. However, there was a recurrence of symptoms after >1 year in 2/9 patients (22%) of Weidenfeld et al.'s patients, but in our study 6/15 (40%) of patients still had symptoms at the time of the interview. One of Weidenfeld et al.'s cases had a father who claimed to experience similar AWS/AWLS symptoms as a child. Five of the nine patients had a family history of migraine or epilepsy. There were also more boys than girls, similar to our study.

The limitations of our study include: incomplete enrollment of eligible patients or their families in the prospective/interview portion of the study, making it possible that any conclusions drawn from this portion of the study are inaccurate; and most often the parents were interviewed, allowing the possibility that some of the follow-up information was incorrect if the child did not report continued symptoms to the parent. In addition, there was likely a small

contribution of referral bias. At our institution, however, pediatric neurologists, pediatric ophthalmologists, and pediatricians have ready access to a pediatric neuro-ophthalmologist and have a low threshold for referring children with neuro-ophthalmic problems, even when the diagnosis is readily apparent. Therefore referral bias is minimized, although it can not be eliminated. In addition, patients with AWS/AWLS due to a cerebral neoplasm or epilepsy may not have been referred to our practice, and this bias would also have influenced our results.

In conclusion, AWS/AWLS typically affects young children, and the most common visual complaints are micropsia and teleopsia. The most common cause is infection, but half of cases have no obvious etiology. Usually symptoms of AWS/AWLS stop eventually, but in over one third of the cases, they continue. One third of patients without a history of migraine may subsequently develop migraine. The results of our study should be extremely helpful to families of young children and their physicians hoping to provide them with diagnostic and prognostic information regarding this unusual condition.

Acknowledgement

The authors would like to thank Drs. Steven Kugler, Sheryl Menacker, Vijay Mudgil, Bruce Schnall, and Martin Wilson for referring many of these patients.

References

1. Liu GT, Galetta SL, Volpe NJ. Visual hallucinations and illusions. In: Neuro-ophthalmology diagnosis and management, 2nd edition. London: Elsevier, 2010:398-399.

2. Carroll L. Alice's Adventures in Wonderland. London: Macmillan, 1865 (downloaded from Apple iBooks August 14 2013)

3. Lippman CW. Certain hallucinations peculiar to migraine. *J Nerv Ment Dis* 1952;116(4):346-351

4. Todd J. The syndrome of Alice in wonderland. *Can Med Assoc J* 1955;73(9):701-704

5. Lanska JR, Lanska DJ. Alice in wonderland syndrome: somesthetic vs visual perceptual disturbance. *Neurology* 2013;80(13):1262-1264.

6. Podoll K, Ebel H, Robinson D, Nicola U. [Obligatory and facultative symptoms of the Alice in wonderland syndrome] (Italian). *Minerva Med* 2002;93(4):287-293.

7. Golden GS. The Alice in wonderland syndrome in juvenile migraine. *Pediatrics* 1979;63(4):517-519

8. Copperman SM. "Alice in Wonderland" syndrome as a presenting symptom of infectious mononucleosis in children: a description of three affected young people. *Clin Pediatr (Phila)* 1977;16(2):143-146

9. Weidenfeld A, Borusiak P. Alice-in-wonderland syndrome--a case-based update and long-term outcome in nine children. *Childs Nerv Syst* 2011;27(6):893-896

Table 1. Patient characteristics of retrospective study (N=48)		
		Comments/Examples
Demographics		
Average age at presentation	8.1 years	Range: 5 years – 14 years
Number of Males	35 (73%)	
Number of Females	13 (27%)	
Visual Symptoms		Some patients had multiple
Teleopsia	24 (50%)	
Pelopsia	5 (10%)	
Micropsia	33 (69%)	
Macropsia	12 (25%)	
Metamorphopsia	7 (15%)	
Movement/Shaking	3 (6%)	
Objects in Three Dimensions	1 (2%)	
Change in one's body image	3 (6%)	
Other related symptoms	1 (2%) -	Sounds much louder than normal
History		
Migraine	7 (15%)	2 had abdominal migraine only
Migraine in Family	22 (46%)	
Seizures	1 (2%)	
AIWS in Family	1 (2%)	
Other	4 (8%)	Asperger's, ADHD, Tourette's, Prematurity
Tests		
Normal MRI	20/21	
Abnormal MRI	1/21	consistent with premature birth
Normal EEG	22/23	
Abnormal EEG	1/23	absence seizures (unrelated)

Etiology of AWS/AWLS		(Some patients had multiple)
Migraine	3 (6%)	
Seizure	0 (0%)	
Infection	16 (33%)	Viral Illness, Strep. throat
Head Trauma	3 (6%)	
Lack of Sleep	1 (2%)	
Lights	2 (4%)	Fluorescent, Strobe
Foods	1 (2%)	
No Cause Found	25 (52%)	

Patient Characteristics of Prospective Study (N=15)	
Interval between initial diagnosis and telephone contact	
Range	2.1-13.53 years
Average	6.5 years
AWS/AWLS symptoms	
More events after diagnosis, but stopped	3 (20%)
No more events	6 (40%)
Still having events at time of interview	6 (40%)
Medical conditions that developed after initial diagnosis of AWS/AWLS	
Migraines	4 (27%)
Seizures	1 (7%)
ADD	1 (7%)
Parents with AWS/AWLS symptoms	5 (33%)