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Neurophysiology of a double aura in migraine and Alice in wonderland syndrome: Is there a link?

Chirchiglia Domenico, Serena Lavano, Pasquale Chirchiglia

University of Catanzaro 1, Department of Neurosurgery, Campus Germaneto, Vle Europa, 88100, Catanzaro, Italy

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ABSTRACT

Objectives: Alice in Wonderland syndrome (AIWS) is a pathological condition characterized by distortions of visual representation, with symptoms deforming images, figures, bodies, objects, which are seen larger or smaller than normal. Causes are sought in infectious diseases, psychiatric illness, migraines. It may be associated with alterations in the body schema such as non-recognition of own body in space. It's a rare form of visual aura. Unlike it, migraine with aura is a very frequent disorder, in which the phenomenon of visual aura is considered a consequence of cortical spreading depression(CSD), a wave of depolarization that propagates from the occipital cortex, creating a vasoconstriction and visual disturbances.

Methods: Recent studies have found an anatomical correlation between visual and somatosensory disorders such as those found in AIWS, located in the temporo- parieto-occipital junction.Neuroimaging studies allowed to identify the CSD and the occipital cortex responsible for the mechanism of the visual aura and the involvement of the parietal cortex in the genesis of the somatosensory aura.

Results: The mechanism of the initiation of the stage of visual and somatosensory aura could be a combination of two events.

Conclusions: Literature data now offer agreed confirmations on the role of the CSD associated to somatosensory aura.

1. Introduction

Alice in Wonderland Syndrome (AIWS) is a perception disorder, involving visual and somesthetic integration. Firstly reported by Todd, on the literary suggestion of the strange experiences described by Lewis Carroll in Alice in Wonderland book (Liu, Liu, Liu, & Liu, 2014). Symptoms may include among others unwareness of self-body image and size distortion such as micropsia, macropsia, pelopsia, or teleopsia, also called dysmetropsias (Eshel, Eyov, Lahat, & Brauman, 1987). This syndrome has many different etiologies; EBV infection is the most common cause in children, while migraine affects more commonly adults (Liu et al., 2014). Techniques of neuroimaging offered a valid contribution to the knowledge of anatomical and functional aspects of this syndrome. Generally parietooccipital brain lobes and, particularly temporoparietal-occipital carrefour (TPO-C) are believed to initiate many of AIWS symptoms (Lahat, Eshel, & Arlazoroff, 1991). AIWS symptoms depend on an alterations of TPO-C where visual-spatial and somatosensory information are integrated. Alterations in these brain regions may cause the coexistence of visual signs,dysmetropsia and disorders of body schema. Cortical spreading depression (CSD) or spreading depolarization is a wave of electrophysiological hyperactivity followed by a wave of inhibition. Spreading depolarization is a phenomenon characterized by the appearance of depolarization waves of the neurons and neuroglia, propagating across the cortex at a velocity of 2–5 mm/min. CSD can be induced by hypoxic conditions and facilitates neuronal death. It has long been recognized the role of CSD in the genesis of migraine aura (Coleman, 1933).

2. Literature review

Alice in Wonderland syndrome (AIWS), named for Lewis Carroll's book, is a disorder characterized by transient episodes of visual hallucinations and distortions of perception, during which objects or body parts are perceived as altered in various ways (metamorphopsia), as enlargement (macropsia) or reduction (micropsia) in the perceived size of a form (Lippman, 1952). It is considered as a form of migraine aura. Aura symptoms include also the perception of flashing lights, scotomas, teicopsias. Symptoms may be somatosensory, such as numbness and tingling in the lips or fingers. They may also involve a profound alteration of the perception of space and time. Regarding etiology, theories point to infections such as the Epstein-Barr virus, medications such as topiramate. Neuroimaging studies have revealed brain regions

E-mail address: chirchiglia@unicz.it (C. Domenico).

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involved in the manifestation of symptoms. These regions include the temporo-parietal-occipital junctions, especially the occipital visual pathways. Blom found up to 30% of adolescents affected out of 169 cases, mostly adults and elderly patients (Podoll & Robinson, 1999). Micropsia and macropsia have been described most frequently in the literature in 58.6% and 45.0% of all patients, respectively. Podoll studied the duration of symptoms of AIWS that tends to be short, mostly on the order of minutes to days; however, symptoms may also persist for years, even be lifelong (Restak, 2006). Clinical studies among patients with migraine indicate that the prevalence rate in this group may be around 15% (Carmichael, 1996). Moreover, some studies indicate that individual symptoms of AIWS are not rare in the general population. A cross-sectional study of 1480 adolescents found a prevalence of micropsia and/or macropsia of 5.6% for males and 6.2% for females (Restak, 2006). Another cross-sectional study of 3224 high school students 32 found 6-month prevalence rates of 3.8% for micropsia, 3.9% for macropsia, 2.5% for protracted duration, and 1.3% for the quick-motion phenomenon (Carmichael, 1996). A third cross-sectional study on 33 of 297 individuals with a median age of 25.7 years found prevalence rates of 30.3% for teleopsia, 18.5% for dysmorphopsia, 15.1% for macropsia, and 14.1% for micropsia. This study also showed that 38.9% of the affected individuals experienced a single symptom, 33.6% experienced two, 10.6% experienced three, and 16.8% experienced four. AIWS is consequence of functional and structural alterations of the perception system (Blom, 2010). Most symptoms of AIWS are attributed to centrally located neuron populations and even cell columns that respond selectively to specific types of sensory input (for vision, cortical areas V1–V5). Area V4 of the extrastriate visual cortex responds selectively to color, whereas area V5 responds to movement. Both areas also respond to shape and depth, but bilateral loss of function of V4 results in achromatopsia (the inability to see color) and bilateral loss of V5 results in akinetopsia (the inability to see movements) (Bui, Chatagner, & Schmitt, 2010; Lanska & Lanska, 2013).

3. Discussion

The term Alice in Wonderland syndrome was introduced in 1955 by the British psychiatrist John Todd (1914–1987) to describe a group of symptoms "… intimately associated with migraine and epilepsy, although not confined to these disorders." (Lahat et al., 1991). The group comprised derealization, depersonalization, hyperschematia, hyposchematia, and somatopsychic duality, as well as illusory changes in the size, distance, or position of stationary objects in the visual field, illusory feelings of levitation, and illusory alterations in the sense of the passage of time. Most cases of AIWS have full remission of the symptoms, sometimes spontaneously and in other cases after treatment, depending on related causes. In clinical practice antiepileptics, migraine prophylaxis drugs, antiviral agents, or antibiotics are used. The literature indicates that antipsychotics are rarely prescribed (Bui et al., 2010; Restak, 2006) since in most cases their effectiveness is considered questionable. Moreover, when distortions are experienced as comorbid symptoms in patients with psychosis, it is important to take into account the possibility that they can sometimes be induced or aggravated by antipsychotics (Willanger & Klee, 1966). The number of case descriptions of AIWS is small, especially considering that the syndrome appears to be underdiagnosed and that individual symptoms may be neglected. Other limitations are the lack of systematic epidemiologic data and limited insight into the many etiologic and pathophysiologic mechanisms possible in this context. Functional imaging techniques such as SPECT and fMRI have the potential to localize the network structures involved in mediating the symptoms of AIWS. Neuron populations have been identified as being responsible for mediating different types of metamorphopsia (Smith, Wright, & Bennett, 2015) or prosopometamorphopsia, in which human faces may be perceived consistently as animal faces and micropsia, which was found to be associated with a consistent pattern of occipital hypoactivation and parietal hyperactivation in an fMRI study (Smith et al., 2015). About somesthetic distortions, aberrations of specific neuron populations in somatosensory cortical areas are responsible for mediating body schema illusions such as microsomatognosia, palisomesthesia, asomatognosia (Abe & Suzuki, 1986). In these cases, parts of the network located around the parieto-temporo-occipital junction are responsible. Whether similar mechanisms are responsible for mediating time distortions is still unknown. The differential diagnosis of AIWS is complex. The symptoms need to be distinguished from other positive disorders of perception such as hallucinations and illusions, with which they may be easily confused In the mechanisms underlying the alterations creating AIWS, there is the involvement of the occipital and parietal lobes. Occipital lobe alterations are responsible for visual disorders such as metamorphopsias, macro-micropsie, while alterations of the parietal lobe cause the lack of spatial location and visual perception. There is a parieto-occipital junction that relates two lobes and explains the combined visual and spatial mechanisms generated by the occipital and parietal cortex, present in the AIWS. In the literature we found as a cause of AIWS a temporo-parietal cavernoma (Abe, Oda, Araki, & Igata, 1989).Cortical Spreading Depression (CSD) is a self-propagating wave of cellular depolarization in the cerebral cortex, the spreading of a wave of oligoemia starting from occipital cortex. The spreading of a wave of vasoconstriction followed by vasodilation causes vasoconstriction of cortical arterioles. The scintillating scotoma of migraine in humans may be related to the neurophysiological phenomenon named the Spreading Depression of Leão (Coleman, 1933). Increased extracellular potassium ion and excitatory glutamate concentration contribute to the initiation and propagation of CSD. It is associated with several pathologic conditions such as migraine and stroke. It was used as a paradigm to evoke transient neuronal depolarization, leading to enhanced energy consumption. Activation of CSD was investigated using spin-lock fMRI (SL), blood oxygenation level-dependent and cerebral blood volume fMRI techniques (Lipsanen, Lauerma, Peltola, & Kallio, 1999). CSD is the subject of study in experimental animals and humans, mainly with brain injury, by investigating cellular events in the meninges shortly after CSD, and using in vivo two-photon imaging to identify changes in macrophages and dendritic cells (DCs) that reside in the pia, arachnoid, and dura. CSD waves in migraine aura patients are observed with the magnet encephalogram (MEG) technique (16). The pathophysiology of CSD explains the appearance of the aura in migraine. It seems that the excitatory action of glutamate during the start of the CSD makes the occipital cortex hyperexcitable (ffytche & Howard, 1999). Occipital and parietal lobes are responsible for both visual and somesthetic auras (Deecke, Mergner, & Plester, 1981; ffytche, Blom, & Catani, 2010).According to a study, a mechanism of abnormal sensory neuronal plasticity would be the cause of AIWS (ffytche et al., 2010). Therefore there would be a link between AIWS and CSD. Both auras, one visual, the other somesthetic, generated from closely related parieto-occipital cortices. A double aura for a double visual-somesthetic disorder.

4. Conclusions

Alice in Wonderland syndrome is a condition characterized by visual and somatosensory disorders, such as the deformation of figures, objects, animals, humans, presenting larger or smaller, or the loss of somatosensory information. It is a visual-sensory aura. The anatomic localization is in the temporo-parieto-occipital lobes. It is also known that the initiation of the visual aura starts from the occipital cortex, with a vasoconstrictive action. It is the cortical spreading depression. Is it possible that the cortical spreading depression could create visual aura in migraine and in the same time could it act together with the parietal cortex in provoking the somatosensory aura in the Alice in Wonderland syndrome? We think that this hypothesis may be suggestive, both for the anatomical and clinical correlations between involved cortical areas.

Conflict of interest and funding

The authors declare no competing interests and no funding.

Ethical statement

On behalf of all authors, the corresponding author states that all ethical aspects are respected.

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