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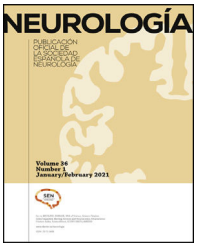

REVIEW ARTICLE

Visual snow syndrome and its relationship with migraine

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Abstract
Introduction: Visual snow syndrome (VSS) is a central nervous system disorder that consists of the constant perception of small black and white dots throughout the entire visual field.
Development: VSS can present from infancy to old age, with greater prevalence in the young population, and shows no difference between sexes. The diagnostic criteria include the presence of visual snow and such other visual phenomena as palinopsia, photophobia, nyctalopia, and other persistent visual phenomena. The pathophysiology of VSS is unknown, but hyperexcitability of the visual cortex and a dysfunction in higher-order visual processing are postulated as potential mechanisms. The prevalence of migraine among patients with VSS is high, compared to the general population, and symptoms are more severe in patients presenting both conditions. No effective treatment is available, but the drug with the best results is lamotrigine, which is recommended only in selected cases with severe functional limitation.
Conclusions: VSS is a little-known and underdiagnosed entity, but the increasing number of studies in recent years has made it possible to establish diagnostic criteria and begin studying its pathophysiology. This entity is closely related to migraine, with overlapping symptoms and probably shared pathophysiological mechanisms.

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PALABRAS CLAVE
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Síndrome de nieve visual y su relación con la migraña

Resume
Introducción: El síndrome de nieve visual (SNV) es un trastorno del sistema nervioso central que implica la visión de forma constante de pequeños puntos blancos y negros en la totalidad del campo visual.
Desarrollo: El SNV puede presentarse desde la infancia hasta la tercera edad, siendo más frecuente en jóvenes y sin diferencia entre géneros. En sus criterios diagnósticos se incluye la presencia de nieve visual, pero también otros fenómenos visuales como palinopsia, fotofobia, nictalopía y otros fenómenos visuales persistentes. La fisiopatología del SNV es desconocida, pero se postulan como mecanismos la hiperexcitabilidad del córtex visual y una disfunción en el procesamiento visual de orden superior. La prevalencia de migraña en los pacientes con SNV es alta en comparación con la población general y cuando se presentan conjuntamente los síntomas son más severos. No se dispone de un tratamiento eficaz, pero el fármaco con mejores resultados es la lamotrigina, recomendándose únicamente en casos seleccionados con alta limitación funcional.
Conclusiones: El síndrome de nieve visual es una entidad poco conocida e infradiagnosticada, pero el creciente número de investigaciones durante los últimos años ha permitido definir unos criterios diagnósticos y acercarnos a su fisiopatología. Es una entidad íntimamente relacionada con la migraña, con solapamiento de síntomas y probablemente mecanismos fisiopatológicos comunes.

Introduction

Visual snow syndrome (VSS) is a central nervous system disorder characterised by the constant perception of small black and white dots across the entire visual field.[1]

Although the phenomenon was first described in 1995,[2] it was not until 10 years later that the expression ''visual snow'' began to appear in the literature.[3] The syndrome has gradually been characterised in recent years, with the first diagnostic criteria being proposed in 2014,[1] and a subsequent update in 2017.[4] VSS involves not only the presence of visual snow but also other visual and non-visual phenomena; this point is addressed below.

Although VSS is a disabling condition, it is frequently underdiagnosed or misdiagnosed as persistent visual aura.[5] Due to the normal results of standard complementary tests, it has even been questioned whether VSS is truly a disease or rather a normal perception of a sensory phenomenon.[6]

Epidemiology

VSS may appear at any age, from childhood to older age, although it is more frequent in young individuals, regardless of sex.[7] Two epidemiological studies were recently conducted in the United Kingdom using an online questionnaire. The first study included 1104 patients reporting visual snow; of these, 1061 were cases of VSS. Approximately 40% had had symptoms for as long as they could remember. Severity varied considerably, with the most severe cases being associated with such comorbidities as migraine and tinnitus.[8] The second study included 1015 patients, of whom 38 (3.7%) had visual snow and 22 (2.2%) had other symptoms suggestive of VSS. Mean age (SD) was 50.6 (14) years; 50% had had symptoms for as long as they could remember, and the remaining 50% presented late onset, with a mean disease duration of 7 years. A total of 339 (33.4%) presented recurrent headache, identified as migraine, and 111 (10.9%) of these had migraine with aura. Tinnitus and mood disorders were more frequent among the patients with VSS.[9] Another recent study found no significant differences between an Italian and a British population.[10]

Symptoms

The main clinical characteristic of VSS is the presence of positive visual phenomena across the entire visual field, described as innumerable tiny flickering dots (visual snow). These dots are typically black and white, but they may also be coloured, flashing, or transparent. Patients may present such other visual symptoms as palinopsia (persistence of an image after the visual stimulus is removed), photophobia, nyctalopia (difficulty seeing in low light), or entoptic phenomena. The lens of the eye has refractive power and can stimulate the visual system, creating entoptic phenomena, which are frequent in the general population; in these patients, however, these phenomena occur daily and are disabling. Examples of entoptic phenomena include floaters (projection onto the retina of the shadows of cell debris floating within the eye's vitreous humour) and blue field entoptic phenomenon (image of white blood cells moving in the retinal capillaries, which intensifies when looking into bright blue light, such as a blue sky).[8]

The non-visual symptoms most frequently associated with VSS are migraine, tinnitus, difficulty concentrating, lethargy, anxiety, depression, balance disorder, and tremor.[7] VSS represents a clinical continuum of varying levels of

severity. The most severe cases are frequently associated with migraine or tinnitus.[8]

Diagnosis

Diagnosis of VSS is clinical and must necessarily rule out ophthalmological or neurological disease. Routine complementary tests (head CT, brain MRI, eye fundus examination, visual field test, visual acuity test, etc) usually yield normal results. Isolated cases have been reported of VSS associated with Creutzfeldt-Jakob disease[11] or anti—glycine receptor antibodies.[12]

The International Classification of Headache Disorders (ICHD) includes VSS among the complications of migraine (A1.4.6 Visual snow) due to its epidemiological association with migraine with aura and the suspicion of a common pathophysiological mechanism.[13]

Diagnostic criteria

1 Persistence of visual snow for > 3 months. Dynamic, continuous perception of uncountable tiny dots across the entire visual field. The dots are usually black/grey on a white background or grey/white on a black background, but may also be transparent, flashing, or coloured.
2 Presence of at least 2 of the following visual alterations:
   a) Palinopsia
   b) Other persistent visual phenomena: excessive floaters in both eyes; excessive blue field entoptic phenomena; self-lighting of the eye (coloured waves or clouds perceived when closing the eyes in the dark); spontaneous photopsia; halos around lights; geometric, coloured lights causing distorted vision; metamorphopsia; straight lines moving across the visual field; images of water.
   c) Photophobia
   d) Nyctalopia
3 Symptoms are not consistent with typical migraine with visual aura.
4 Symptoms are not better accounted for by another disorder. Normal neuro-ophthalmological examination results (including corrected visual acuity, dilated-pupil fundoscopy, visual field examination, electroretinography, and even visual evoked potentials). No intake of toxic substances or psychotropic drugs.

These criteria, proposed in 2017,[4] continue to be used in the ICHD,[13] although some changes were implemented in 2018 regarding diagnostic criterion 2b, ''enhanced entoptic phenomena,'' which in the more recent version encompasses other types of visual alterations that were previously unclassifiable.[14]

Pathophysiology

The pathophysiology of VSS is unknown, and several mechanisms have been proposed; the location where VSS originates is the most relevant question. The fact that the entire visual field is involved makes it unlikely that the syndrome is caused by a lesion to the visual pathways (retina, optic nerve, optic nerve, optic chiasm, optic pathway, lateral geniculate nucleus, optic radiations) or to the primary visual cortex, which present a monocular or homonymous organisation. The symptoms of VSS, frequently associated with palinopsia or enhanced entoptic phenomena, suggest involvement of visual processing in the extrastriate cortex, downstream from the primary visual cortex.[15]

This hypothesis is reinforced by FDG-PET findings in patients with VSS, which reveal marked hypermetabolism in the right lingual gyrus (visual supplementary cortex, Brodmann area 19) and a trend in the left cerebellum.[16] Furthermore, a study using FDG-PET and volumetric MRI observed hypermetabolism and increased cortical volume in the extrastriate visual cortex at the junction of the right lingual and fusiform gyri.[17] Another study with volumetric brain MRI concluded that patients with VSS present increased grey matter volume in the left primary and secondary visual cortices, the left visual motion area V5, and the left cerebellum.[18] A study using blood oxygen level—dependent functional MRI detected decreased activation of the anterior insular cortex in response to visual stimuli in patients with VSS. The anterior insula is essential in selecting relevant information from the vast number of stimuli that are constantly received and processed, and subsequently transmitted to other areas of the limbic system. Dysfunction in this area may explain why stimuli that would normally be considered irrelevant are perceived as normal. This study also used spectroscopy and found increased lactate concentrations in the right lingual gyrus of patients with VSS, suggesting metabolic hyperactivation.[19]

The neuroimaging findings mentioned above suggest involvement of the extrastriate visual cortex. However, there are discrepancies in the reported electrophysiological evidence regarding the localisation of the dysfunction in the striate or extrastriate visual cortices. Some studies using visual evoked potentials suggest dysfunction of the visual association cortex (increased N145 latency), with preservation of the primary visual cortex (normal P100 time and visual evoked potential habituation),[1,20] while others suggest hyperexcitability of the primary cortex due to loss of visual evoked potential habituation,[21] low phosphene thresholds in the left occipital lobe with transcranial magnetic stimulation,[22] or reduced gamma-band power on EEG (suggestive of diminished inhibitory activity).[23]

In a behavioural analysis including 4 visual tasks stimulating different central areas involved in visual coding and processing, aberrant excitability was observed in the primary visual cortex (contrast, luminance) in patients with VSS, with no alterations in the visual association cortex (form, motion).[24]

Another study with colorimetry revealed that the yellow-blue colour spectrum improved symptoms in 10 of 12 patients with VSS. This led the researchers to hypothesise that VSS is a disorder of central colour-dependent processing involving the magnocellular pathway, and suggested thalamocortical dysrhythmia as the underlying pathophysiological mechanism.[25]

Studies have also addressed the model of stochastic resonance, in which the addition of noise enhances the recognition of weak stimuli, even in different sensory modal-

ities. This model may explain the presence of such other visual and non-visual symptoms as tinnitus or photophobia.[14]

In summary, the pathophysiology of VSS is believed to be associated with visual cortex hyperexcitability and higher-order visual processing dysfunction, although the localisation is still debated. More specifically, it is unclear whether the disease involves the primary visual cortex (striatum), visual association cortex (extrastriate), or the thalamocortical pathway.[26]

Association with migraine

Visual aura, the most common type of aura, occurs in 90% of patients with migraine with aura. It is a transient and reversible phenomenon, which appears gradually and lasts 5 to 60 minutes. It typically precedes pain, although it can also appear during or after a migraine attack, or even in isolation. The visual pattern of an aura is frequently described as a fortification spectrum (flashing lights following a simple zigzag pattern or a polygonal form resembling the walls of a medieval fort) that expands from the centre of the visual field to the periphery, leaving a scotoma in its path (or in reverse order). Despite this classical description of visual aura, flashing lights are the most frequently reported visual alteration. Other visual phenomena include dots, wavy lines, blind spots, and tunnel vision.[27] These are usually short-lived; when they persist longer, they are classified in the ICHD as complications of migraine (in the same way as with VSS) in the form of persistent aura without infarction or migraine aura status.[13,15]

Persistent aura is typically visual, defined as symptoms lasting longer than a week without radiological evidence of infarction. These patients must have history of migraine with aura, and the persistent aura must present similar characteristics to those of previous auras.[13] Persistent auras are rare, and symptoms are usually bilateral, lasting for several months or even years. These persistent auras may be described as bright colours, wavy lines, sparkles, or dots. Episodes of aura with at least one symptom lasting more than an hour but less than a week can be labelled as prolonged aura, although this term is no longer used in the ICHD, with these episodes being classified as probable migraine since the criteria for typical aura are not met. In the event of prolonged or persistent aura, prothrombotic states and stroke should be ruled out with neuroimaging studies.[28—30]

Migraine aura status is defined in the ICHD as the occurrence of at least 3 episodes over a minimum of 3 consecutive days, after excluding such secondary forms as reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, and artery dissection.[13]

Differentiating VSS from persistent migraine aura can be a challenge, as some symptoms are common to both conditions, including palinopsia, photophobia, nyctalopia, and tinnitus.[16,31,32] In migraine, visual alterations are typically homonymous and do not affect the entire visual field. The symptoms of VSS, in contrast, have a more rapidly and dynamically changing nature, and are global (visual flickering), monocular, or differ between the 2 eyes (entoptic phenomena).[15] The prevalence of migraine, with or without aura, is higher among patients with VSS than in the general population. In a study including 120 patients with VSS, 58% had migraine and 31% had typical visual aura.[16] In another study, mentioned above, 54.5% of patients with VSS reported headache lasting > 4 hours (22.7% of these presented characteristics of migraine with visual aura), compared to 33% of patients without VSS (10.7% with characteristics of migraine with visual aura).[9]

Several studies support the hypothesis that patients with migraine aura present cortical hyperexcitability,[33,34] and neuroimaging studies have shown that the lingual gyrus is involved in photophobia during migraine[35,36]; these data suggest that VSS and migraine share several pathophysiological mechanisms that may justify the frequent association between the 2.

Patients with VSS and associated migraine present higher numbers of additional symptoms (photophobia, palinopsia, photopsia, nyctalopia) and comorbidities (tinnitus and depression), which suggests that migraine may worsen the clinical presentation of VSS.[8,9,16]

Differential diagnosis

Visual alterations are commonly seen in clinical practice, but not all positive visual phenomena originating outside the retina are caused by migraine. VSS may be misdiagnosed for entities other than migraine with visual aura. Transient ischaemic attack typically presents suddenly and is associated with such negative symptoms as transient monocular vision loss (amaurosis fugax) and hemianopia. In occipital lobe epilepsy, visual alterations are repetitive and stereotyped, lasting from seconds to minutes, in the form of small, flashing, brightly-coloured spots or shapes.[27]

Hallucinogen-persisting perception disorder refers to the spontaneous recurrence of visual alterations (geometric shapes, objects in the peripheral visual fields, flashes of different colours, palinopsia, etc) attributed to acute hallucinogen intoxication.[37]

Charles Bonnet syndrome is characterised by impaired vision as the result of a lesion to the anterior visual pathway; patients experience visual hallucinations in the form of complex, non-threatening images (eg, faces, animals, or objects), but also report geometric hallucinations consisting of coloured patterns, spots, and shapes.[27]

Treatment

Due to the lack of randomised clinical trials, all available data are from case series in which patients are treated with medications for migraine prophylaxis (topiramate, propranolol, verapamil, valproate), antidepressants (sertraline, amitriptyline), or other drugs (naproxen, lamotrigine, baclofen), which show poor effectiveness and may even exacerbate symptoms (as in the case of amitriptyline).[38] The best treatment option is lamotrigine,[21,39] although it only achieves partial remission and has adverse effects; therefore, it is only recommended in select cases associated with severe functional limitation. A retrospective review of 58 cases of VSS reported partial improvements in 5 of 26 patients, with 13 presenting adverse effects; therefore, only 4 patients opted to continue treatment.[40]

In the light of the above, it is unsurprising that most patients do not receive treatment, or discontinue it due to adverse effects. Despite the lack of an effective treatment for VSS, the associated comorbidities (eg, migraine, depression) should be managed. As mentioned previously, the use of colour filters in the yellow-blue spectrum has been proposed to reduce symptoms.[25] As these patients present chronic symptoms and have a long history of attending consultations with a wide range of specialists, the simple fact of acknowledging the syndrome and reassuring them about its benign nature may help to alleviate their suffering.

Conclusions

VSS is a little-known and underdiagnosed entity. However, the increasing number of studies conducted in recent years has led to the development of diagnostic criteria and provides a better understanding of its pathophysiology. There is considerable clinical overlap between VSS and migraine, which probably have common pathophysiological mechanisms. Unfortunately, no effective treatment is currently available for VSS.

Conflicts of interest

The authors have no conflicts of interest to declare.

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