The phenomenon of "visual snow": clinical and pathophysiological correlations, differential diagnosis and treatment (literature review)

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Visual snow syndrome (VSS) is a visual perception disorder characterized by persistent positive visual symptoms described by patients as "tiny dots, pixel vision, interference as on TV". To date, the prevalence of VSS may be as high as 2.2–3.7% of the population, which significantly increases the interest not only of physicians but also of medical researchers. In addition, patients may have other visual symptoms as well as tinnitus, migraine, dizziness, tremor, fibromyalgia, paresthesias, depersonalization, derealization, anxiety, and depression. VSS may affect quality of life, educational, professional and social activities. The article discusses the criteria for diagnosis, pathogenesis, differential diagnosis, clinical cases, and approaches to the treatment of VSS.

Keywords: *"visual snow"; "visual snow" syndrome; migraine; thalamocortical dysrhythmia; epilepsy; ischemic stroke; retinitis pigmentosa.*
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For reference: *Kamaeva AS, Kiryanova EA, Tabeeva GR. The phenomenon of "visual snow": clinical and pathophysiological correlations, differential diagnosis and treatment (literature review). Nevrologiya, neiropsikhiatriya, psikhosomatika = Neurology, Neuropsychiatry, Psychosomatics. 2023;15(5):65–71.* ***DOI:*** *10.14412/2074-2711-2023-5-65-71*

Visual snow syndrome (VSS) is considered a rare pathology, but recent studies have shown that it can occur in up to 2.2–3.7% of the population [1–4]. For a long time, the phenomenon of "visual snow" (VS) was regarded as a persistent visual aura of migraine or as a manifestation of a psychiatric disorder. It was not until 1995 that G.T. Lui et al. [5] described it as "persistent positive visual phenomena" and publications from 2012 to 2014 first applied the term "visual snow syndrome" due to a more common impairment of sensory information processing compared to migraine visual aura [1].

In 2014, for the first time in the neurological journal «Brain» criteria for VSS were proposed, which were subsequently implemented in the 3rd revision of the International Classification of Headache Disorders (ICHD) in 2018 for the differential diagnosis of visual phenomena (especially in migraine with aura) [6].

The diagnosis of VSS is based on persistent "TV interference" or "pixelization" in the form of moving colored or black and white dots across the visual field for more than 3 months, and the presence of two of the following four symptoms: 1) photophobia (feeling of discomfort or pain when experiencing normal light); 2) enhanced entoptic phenomena (perception of visual phenomena inside the eye: Shearer or blue field phenomenon, moving whitish structures when looking at a blue background or the sky in the field of vision; floating "flies" in front of the eyes; photopsia – flash-like visual phenomena; perception of light or colored "clouds" through closed eyes); 3) palinopsia (visual perseveration or visual trace of an object that is no longer in the visual field, visual traces behind moving objects); 4) nyctalopia (impaired vision in the dark or "night blindness"), except for the symptoms consistent with migraine aura or symptoms occurring secondary to, for example, substance use [7–9].

The most frequently reported symptoms in patients with VSS are palinopsia (94%), nyctalopia (72%), and photophobia (61%); of the non-visual symptoms, tinnitus (94%), tremor (50%), and migraine (39%) were reported [8].

The severity of VSS is also determined by the number of associated symptoms and diseases. In addition, dizziness, fibromyalgia, depersonalization, derealization, anxiety, and depression may accompany VSS. The results of the study by E.J. Solly et al. [10] (n=125) showed that VSS significantly affects the quality of life of patients; sleep disturbance, fatigue and anxiety can lead to an increase in VSS, while improving sleep and reducing stress can improve the course of VSS. It has been observed that the combination of VSS and migraine is associated with more severe visual symptoms [10, 11].

Conditions and diseases associated with VSS

Secondary VSS can be associated with medications, substance use, occipital epilepsy, stroke, brain injury (with VSS onset immediately or within 3 months after the injury), multiple sclerosis, tumor, degenerative diseases (e.g., posterior cortical atrophy), idiopathic intracranial hypertension, rigid-man syndrome, etc. [12–15].

Migraine with aura and VS. The clinical symptoms of VS differ from typical characteristics of a migraine aura: VS extends over the entire visual field, is not characterized by a

gradual development of the symptom depending on the spreading cortical depression (depolarization wave), lacks the classic features of migraine, and is not amenable to therapy with many antimigraine drugs. Nevertheless, migraine is a common comorbidity in VSS [5, 6, 11, 16–19]. It has been hypothesized that VSS and migraine aura are associated with increased excitability of certain brain neural networks. I. Unal-Cevik et al. [18] described an unusual type of VS: it was episodic (in most patients with VSS it is constant) and associated with migraine attacks without any other additional visual symptoms. In contrast to regular VSS, episodic VS corresponded to the migraine pattern. This symptom occurs in less than 0.2% of migraine patients [19].

Ischemic stroke. T. Catarci [20] described the transformation of episodic VSS into persistent one in a 74-year-old patient after ischemic stroke caused by occlusion of the right posterior cerebral artery with the development of left-sided superior quadrant hemianopsia. F. Puledda et al. [2] published a case report on the transformation of episodic VS into permanent one in a 44-year-old man after the development of stroke in the vertebral-basilar basin against the background of right vertebral artery dissection. Conversely, there is evidence that a 25-year-old woman experienced transient resolution of VSS within a week after a hemorrhagic stroke in the left thalamic region [21].

Retinal pathology. A. Tuekprakhon et al. [22] presented a unique combination of X-linked retinitis pigmentosa (p.Glu809GlyfsTer25) and a symptom similar to VS in an 8-year-old female patient. The girl reported consistently seeing persistent multicolored dots and spirals throughout her visual field (Fig. 1) for as long as she could remember, a symptom resembling pulsatile VS, which she described as "flickering dots throughout her visual field," with no history of migraine, head injury, or epilepsy.

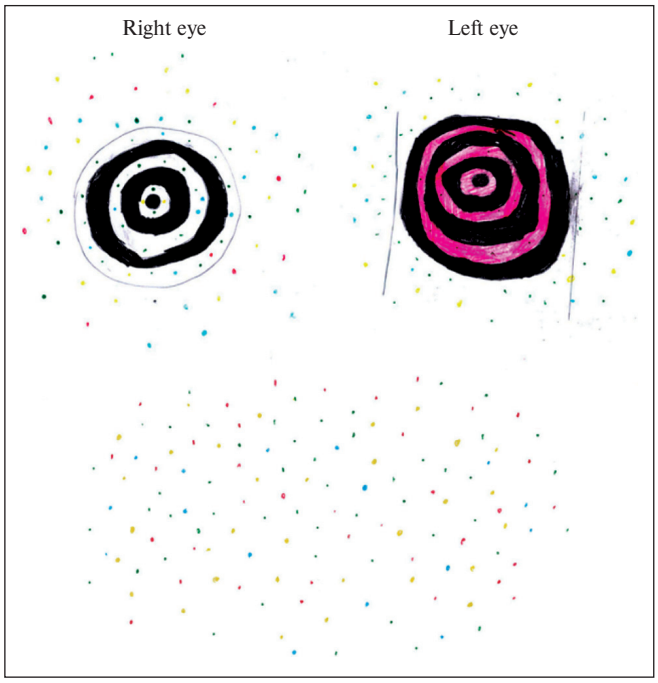

Fig. 1. *Drawing of an 8-year-old female patient with X-linked retinitis pigmentosa describing her visual symptoms (from [22]). above — black-and-white or coloured swirls with colourful dots; below — colourful dots involving the entire visual field*

According to a report by D.J. Mehta et al. [21], 7 out of 98 people with secondary VSS were found to have yellow spot atrophy, central serous chorioretinopathy, vitreous detachment and multifocal choroiditis with yellow spot lesions, as well as optic nerve atrophy. Y.J. Yoo et al. [23] noted that 8 out of 28 patients with VSS have cone and rod dystrophy. They described a typical case of this pathology misdiagnosed as idiopathic VSS: a 36-year-old woman with migraine without aura suffered from VSS for 6 months, while she had normal visual acuity, ocular fundus; a binasal visual field defect was detected; electroretinography showed sharply reduced scotopic response and relatively preserved photopic response. A.K. Bittner et al. [24] demonstrated that VSS was present in 22% of patients with retinitis pigmentosa. It is assumed that VS in this case results from spontaneous discharges from the remodeled inner layer of retinal nerve fibers.

Posterior uveitis can also manifest in VS. For example, VS has been described during steroid treatment for multifocal choroiditis with yellow spot involvement. VS can also occur in birdshot chorioretinopathy, which is a rare variant of posterior chronic bilateral autoimmune uveitis closely related to HLA-A29 [25].

Thus, clinicians should be able to perform a thorough ophthalmologic screening, including an electroretinogram, and refer patients to genetic testing when necessary.

Drug-induced VS. VS caused by synthetic drugs includes hallucinogen persisting perception disorder (HPPD) and the effects of drugs such as proton pump inhibitors, imiquimod, ciprofloxacin, tamoxifen, amantadine, testosterone, escitalopram, duloxetine and bupropion, and intravenous glucocorticoids [14]. For example, O.E. Eren et al. [26] reported a 31-year-old woman with episodic migraine and VSS after taking 20 mg of citalopram daily for 2 weeks, and VSS persisted after discontinuation of the drug.

Hallucinogen-persisting perception disorder (HPPD) is a repeated experience of altered sensory perception similar to the symptoms caused by hallucinogen use. HPPD is mainly caused by lysergic acid diethylamide, cannabis, synthetic cannabinoids, phencyclidine, ecstasy, psilocybin, mescaline, and methamphetamine. HPPD is divided into two types: type I is short-term, characterized by a benign course, mild involuntary recurrent memories, not leading to significant anxiety and difficulties in the social sphere; type II is characterized by severe impairment, prolonged course, irreversible or slowly reversible symptoms; many patients are unable to adapt to life without medication [27]. In type II HPPD, occurring in 0.002% of people who have used hallucinogens, persistent VSS, palinopsia, and halos appear. Ophthalmologic and neurologic examinations do not reveal any features in these patients. H. Schatten et al. [28] described a 24-year-old woman with constant "snow-like" flickering before her eyes for 1.5 years after using a cocktail of amphetamines, hallucinogens, and alcohol. A thorough examination revealed no abnormality, which confirmed the diagnosis of HPPD type II.

One possible cause of HPPD is excitotoxic damage to inhibitory interneurons [27]. To date, no standardized clinical guidelines have been developed regarding the therapy of HPPD; the use of presynaptic α_2-agonists, benzodiazepines, anticonvulsants, and low-dose first-generation neuroleptics has been reported [14].

Possible mechanisms of VSS pathogenesis

Currently, the accumulated results suggest the presence of a neural network visual disorder involving pre-cortical and attention networks, where "filtering" of incoming information takes place [8, 13, 29]. F. Puledda et al. [30] found changes in regional blood flow in the superior parietal lobule, inferior parietal lobule, angular gyrus, precuneus and cuneiform body of both hemispheres, as well as in the occipital cortex during VSS. The parietal cortex is known to play a fundamental role in the integration of various sensory stimuli. Specifically, the dorsal visual pathway carries visual information from the primary visual cortex to the posterior parietal lobe and on to other integrative brain regions. In the above study, an increase in regional cerebral blood flow was shown in the area of the dorsal visual pathway, Brodmann field 8 (analyzing visual information and proprioception). The precuneus and posterior cingulate cortex constitute the posterior elements of the passive mode network of the brain (an organized mode of brain functioning that is active at rest and "suspended" during certain purposeful actions – the passive mode network of the brain). Considering that there is a bilateral increase in blood flow in these areas, this could potentially indicate increased functional activity in the passive brain mode network in patients with VSS. The anterior precuneus region, angular gyrus, are typically activated during cognitive tasks, during control of visually guided movements, and during visual-proprioceptive integration. The more medial regions of the precuneus are also an element of the frontoparietal network which specializes in external attention and visual-spatial perception. It is assumed that the involvement of these brain regions in VSS leads to "overattention" to common sensory stimuli [30].

A genetic predisposition to neuronal hyperexcitability is also being considered. Increased activation of serotoninergic receptors has been reported in HPPD and migraine. These receptors receive serotonergic signals from axons of neurons of suture nuclei that go to the primary visual cortex (V_1). Neurons that are possibly involved in the etiology of HPPD are inhibitory cortical interneurons that express 5-HT_{2A} receptors and release GABA upon activation. It is hypothesized that when these neurons are damaged, various symptoms appear, including VSS, and internal noise is transmitted as a signal that would normally be suppressed. Thus, there is imbalance between the inhibitory and excitatory input of visual information processing [31].

L. Michels et al. [32] found changes in fractional anisotropy values in prefrontal, temporal, and occipital regions during magnetic resonance imaging (MRI) and suggested that atypical visual processing may be an important mechanism of VSS.

A case of VSS on the background of ischemic stroke in the cerebellar hemisphere described by F. Puledda et al. [2] indicates the involvement of the cerebellum in the pathophysiology of VSS. The posterior cerebellum is known to play a key role not only in motor functions but also in sensorimotor and cognitive integration.

Patients with VSS demonstrated a lower threshold of excitability and lack of habituation to phosphenes compared to controls during transcranial magnetic stimulation of the occipital cortex. [33, 34].

Another area involved in the pathogenesis of VSS is probably the dorsal visual network or motor network, which is located dorsally from V_1 to the parietal lobe and includes the region of motion (V_5) at the temporo-parieto-occipital junction. Dysfunction in visual motion processing possibly plays a role in the perception of static dots as moving. This area may also be associated with seeing a "trail" behind a moving object. In the visually active state, the dorsal visual network and V_5 showed hyperintegration with other brain regions in patients with VSS [35].

J.L. Hepschke et al. [36] suggested that VSS may be characterized by a disturbance in the rhythmic activity of the visual system. Magnetoencephalography was used to test 18 patients diagnosed with VSS and 16 individuals who constituted the control group. The participants were presented with visual grating stimuli that induce attenuation of the alpha rhythm (8–13 Hz) and enhancement of the gamma rhythm (40–70 Hz). In both groups, decreased alpha rhythm power and increased gamma rhythm power were localized in the primary visual cortex. Patients with VSS demonstrated a significant increase in gamma rhythm in the primary visual cortex area ($p=0.035$), which is consistent with previous MRI and positron emission tomography brain imaging findings in VSS. A significant decrease in alpha-gamma rhythm coupling was found in the VSS group ($p<0.05$), indicating a potential excitation-inhibition imbalance in VSS, as well as a potential impairment of the descending "noise reduction" mechanism. Overall, these results suggest hyperactivity of the primary visual cortex during VSS.

Anomalies of white matter of the brain. A study by L. Michels et al. [32] clearly show changes in the white matter of the brain in the visual, frontal and temporal lobes. When comparing the results obtained with and without adjustment for migraine and tinnitus, changes in the inferior fronto-occipital fasciculus, sagittal layer, and right superior longitudinal fasciculus were registered. The authors hypothesize that these particular anomalies may be related to atypical visual processing of incoming information and VSS. The sagittal layer represents the cortical-subcortical pathway from parietal, occipital, temporal regions to the thalamus, brainstem nuclei, and is possibly involved in processing visual information at the level of the lateral patellar body (subcortical structures).

F. Puledda et al. [30] conducted an MRI study of changes in regional cerebral blood flow in 24 patients with VSS compared to healthy subjects. A localized increase in regional cerebral perfusion in patients with VSS was found in a vast brain network that includes the cuneus, precuneus, supplementary motor cortex, premotor cortex, and posterior cingulate cortex, as well as the left primary auditory cortex, spindle gyrus, and cerebellum.

Thalamic dysfunction. A characteristic property of the thalamocortical system is oscillatory network activity (thalamocortical resonance), which is central to cognitive processes such as attention and perception [19]. Alterations in these oscillations, particularly the amplification of low-frequency delta and theta rhythms in the waking state, are commonly referred to as thalamocortical dysrhythmias, which are thought to cause a number of symptoms associated with impaired sensory processing. Migraine and tinnitus, for example, are considered a consequence of thalamocortical dysrhythmias. There is a suggestion that VSS may be a form of

thalamocortical arrhythmia [37]. Similarly, retinal dysfunction can lead to disinhibition of projection pathways from the thalamus to the primary and secondary visual cortex. It should be noted that wearing special colored glasses helps some patients with VSS. In addition, patients with VSS show an aversion to violet hues, which increase S-cone excitation. Viewing a visual stimulus through a violet-tinted filter significantly exacerbates VS symptoms, so it is hypothesized that signals from S-cones traveling through coniocellular pathways influence the appearance of dysregulation in the thalamocortical system [37].

Treatment

VSS therapy remains a stumbling block up to the present day. In general, the course of VSS is more often stable, although the severity of its symptoms can vary considerably, reducing patients' ability to work. A long history of VSS does not usually result in any complications. In case of secondary VS, the underlying disease is treated [21, 38–41].

Several studies have reported that some patients showed partial regression of VS symptoms when receiving benzodiazepines, lamotrigine, topiramate, and acetazolamide. In a review of articles on the treatment of VSS, only eight of 44 medications were sometimes effective: lamotrigine, topiramate, valproic acid, propranolol, verapamil, baclofen, naproxen, and sertraline. Lamotrigine was effective in eight of 36 cases (22%), topiramate in two of 13 (15.4%) [28].

F. Puledda et al. [39] evaluated the response to treatment and the course of symptoms in 400 patients with VSS (patients indicated the medications prescribed by their clinicians). One third of patients (35%; n=139) had suffered from persistent VS since early childhood.

Also F. Puledda et al. [39] collected information on 154 different pharmaceutical and nutraceutical preparations, including caffeine, narcotic substances (16 cases), and alcohol (Fig. 2). The most commonly mentioned medications used by patients were antidepressants, antiepileptics, antibiotics, benzodiazepines, narcotics, and vitamins. Vitamins and nutraceuticals had the highest therapeutic ratios, although they conversely had no effect on symptoms in 80% of cases, as did benzodiazepines and sleeping pills. This study shows a lack of effect in most cases of VSS therapy. Randomized controlled trials are needed to evaluate the efficacy of drugs such as benzodiazepines, lamotrigine, and topiramate, especially since the efficacy of antiepileptic drugs has been virtually 1:1 for both improvement and worsening of VSS.

The results of the effectiveness of rhythmic transcranial magnetic stimulation in patients with migraine have been contradictory [8, 33, 34].

It is also possible to slightly reduce the VSS with customized tinted lenses. When blue-yellow spectrum filters were selected, patients were more likely to report subjective improvement in symptoms [8].

Considering that psychiatric symptoms are frequently reported in patients with VSS and are associated with increasing severity of visual symptoms and decreased quality of life, treatment of anxiety and depression may offer an opportunity to improve patients' quality of life. Of note, visual symptoms may worsen with the use of antidepressants (especially citalopram) that inhibit serotonin reuptake, with 8.9% of patients reporting VS, 10.5% reporting palinopsia, 15.3% reporting photophobia, and 17.7% reporting nyctalopia as a side effect of the drug. Amitriptyline is also capable of worsening the course of VSS [8].

Tinted lenses, psychotherapy, selective serotonin reuptake inhibitors (escitalopram), anticonvulsants (lamotrigine), benzodiazepines (lorazepam and clonazepam), and norepinephrine reuptake inhibitors, have been used to treat HPPD. Complete regression of VSS has been reported with benzodiazepines, partial regression with selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and combination therapy: psychotherapy + lamotrigine + lorazepam (2 years) and clonazepam + escitalopram [12, 42–44].

Conclusion

Thus, VSS is probably a disorder associated with neural network dysfunction, which manifests itself in impaired interaction between different parts of the visual system and related structures and causes reduced inhibitory modulation / phenomena of their hyperactivity. VSS is often undiagnosed, causing difficulties in patient management, just as pediatric equivalents of migraine [45], drug-induced headache [46, 47], and vestibular migraine [48]. Often VSS is benign in nature and does not lead to any complications. But untimely diagnosis of secondary causes of VS can lead to irreversible consequences, so it is necessary to collect a detailed history, and conduct appropriate diagnostic tests (neuroimaging, thorough ophthalmologic examination) to exclude them. Currently, therapeutic approaches to this condition have not been developed, and many drugs used in the treatment of VSS may also worsen its course. Understanding the topical distribution of the neural network involved in pathogenesis may lead to the development of new therapies for VSS, such as neuromodulation.

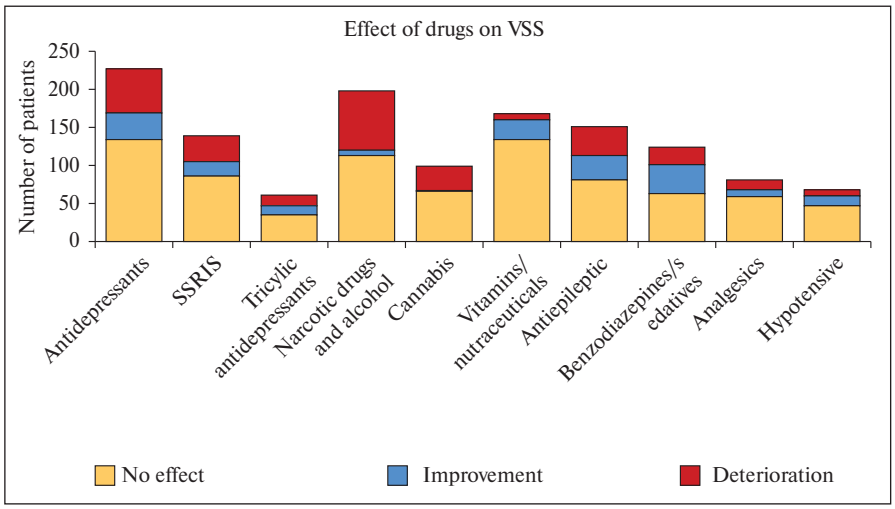

Fig. 2. *Results of a survey of 380 patients with SHS (according to [39], with modifications)*

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Received/Reviewed/Accepted
03.05.2023/12.07.2023/14.07.2023

Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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