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Neuro-ophthalmologic Findings in Visual Snow Syndrome

Yung-Ju Yoo[a*]
Hee Kyung Yang[b*]
Jeong-Yoon Choi[c]
Ji-Soo Kim[c]
Jeong-Min Hwang[b]

[a]Department of Ophthalmology, Kangwon National University Graduate School of Medicine, Kangwon National University Hospital, Chuncheon, Korea
[b]Departments of Ophthalmology and [c]Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Background and Purpose The findings of ophthalmic examinations have not been systematically investigated in visual snow syndrome. This study reviewed the abnormal neuro-ophthalmologic findings in a patient cohort with symptoms of visual snow syndrome.

Methods We retrospectively reviewed 28 patients who were referred for symptoms of visual snow to a tertiary referral hospital from November 2016 to October 2019. We defined the findings of best corrected visual acuity (BCVA), visual field testing, pupillary light reflex, contrast sensitivity, full-field and multifocal electroretinography, and optical coherence tomography.

Results Twenty patients (71%) were finally diagnosed as visual snow syndrome. Their additional visual symptoms included illusionary palinopsia (61%), enhanced entoptic phenomenon (65%), disturbance of night vision (44%), and photophobia (65%). A history of migraine was identified in ten patients (50%). The mean BCVA was less than 0.1 logarithm of the minimum angle of resolution, and electrophysiology showed normal retinal function in all patients. Contrast sensitivity was decreased in two of the seven patients tested. Medical treatment was applied to five patients which all turned out to be ineffective. Among the eight patients who were excluded, one was diagnosed with rod-cone dystrophy and another with idiopathic intracranial hypertension.

Conclusions Neuro-ophthalmologic findings are mostly normal in patients with visual snow syndrome. Retinal or neurological diseases must be excluded as possible causes of visual snow.

Key Words visual snow, electrophysiological phenomena, cortical excitability, migraine, optical coherence tomography.

INTRODUCTION

Visual snow is an uncommon phenomenon that is characterized by the perception of TV static-like "snow" in the entire visual field.[1] Cortical hyperexcitability and thalamocortical dysrhythmia are potential mechanisms for explaining the persistent symptoms.[2,3] In addition to visual snow persisting for more than 3 months, the International Headache Society diagnostic criteria specify that patients must also have at least two of the following symptoms: excessive entoptic phenomenon, palinopsia, photophobia, and nyctalopia.[4,5] While visual snow syndrome is typically benign,[4] it occasionally appears as the first symptom of serious neurological diseases such as the Heidenhain variant of Creutzfeldt-Jakob disease.[6] Beside neurological diseases, retinal diseases, persistent migraine aura, and hallucinogenic drugs must be excluded as possible causes of visual snow and palinopsia—visual snow syndrome must be diagnosed by exclusion after a thorough ophthalmic examination.[7]

There are a few case series that have described ophthalmological findings of visual snow. However, none of these previous reports have included pupillary light reflex and contrast sensitivity in these patients, whereas both of these measurements are reported to be abnormal in patients with migraine visual aura.[8,9] Since visual snow is suggested to share some pathophysiological mechanisms with migraine visual aura, these parameters may help in

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Correspondence
Jeong-Min Hwang, MD
Department of Ophthalmology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro, 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel +82-31-787-7372
Fax +82-31-787-4057
E-mail hjm@snu.ac.kr

*These authors contributed equally to this work.

identifying visual snow syndrome and inferring the underlying pathophysiology.

This study examined the ocular characteristics of 20 patients with visual snow syndrome, including the pupillary light reflex, contrast sensitivity, and electrophysiological studies, as well as the clinical features of comorbid diseases and treatment responses. Atypical neuro-ophthalmologic findings in patients with visual snow syndrome are reported.

METHODS

Study subjects

We performed a retrospective review of patients referred to a neuro-ophthalmology outpatient clinic with "positive visual disturbance" between November 2016 and October 2019. Previously published standard criteria were used after being translated into Korean.[4] The translation of each term was performed by a neuro-ophthalmologist following the standard English-Korean terminology provided by the Korean Medical Association.[10] Each visual symptom mentioned in the English version criteria was associated to a Korean term. This translation was checked by two neuro-ophthalmologists, and then other translaters performed a back-translation into English. The English and Korean versions were reconciled based on the agreement of two neuro-ophthalmologists. Visual snow was diagnosed according to the following recently proposed criteria:[4] 1) dynamic, continuous visual snow for more than 3 months; 2) at least two additional visual symptoms among palinopsia, entoptic phenomena, photophobia, and nyctalopia; 3) symptoms not consistent with typical migraine with visual aura; and 4) symptoms not better explained by other disorders or psychotropic drugs. Patients were diagnosed as having migraine and/or typical migraine aura based on the judgment of two neurologists. Migraine was diagnosed based on the third edition of the International Classification of Headache Disorders beta version.[5] Medical charts and referral letters were reviewed to identify a previous diagnostic history of anxiety and depression. Medical charts were also reviewed to extract data on demographics, medical and psychiatric comorbidities, neurological examination results, and prescribed medications.

Regarding pharmacological treatment, drug dosage, adverse events, symptom resolution, and decisions to continue were reviewed. Complete remission was defined as the disappearance of visual snow, while partial remission was defined as an improvement in the self-assessed symptom severity.[11]

Ophthalmic examinations

Ophthalmic examinations included assessments of the best corrected visual acuity (BCVA), automated refraction, slit-lamp biomicroscopy, and dilated fundus examinations. Patients underwent standard automated perimetry measurements: central 24-2 threshold test of the Humphrey visual field (Humphrey Instrument, Inc., San Leandro, CA, USA). The thickness of the retinal nerve fiber layer (RNFL) was assessed using spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany). Automated monocular pupillometry (PLR-200, NeurOptics, Irvine, United States) was used to record the following parameters of the pupillary light reflex: pupil diameter, latency, constriction ratio, and constriction velocity.[12] Full-field electroretinography (ERG) and multifocal ERG (mfERG) were performed in accordance with established standards.[13,14] Spatial contrast sensitivity was assessed using the Functional Acuity Contrast Test (F.A.C.T.™) (Stereo Optical Company, Chicago, United States) at a distance of 3 m.[8] The F.A.C.T.™ consists of a chart with sine-wave gratings of varying frequencies, and tests five spatial frequencies (sizes) and nine levels of contrast. The F.A.C.T.™ reference values (85 cd/m^2 and 3 cd/m^2) have been established in a healthy population with an uncorrected visual acuity of at least 0.00 logarithm of the minimum angle of resolution (logMAR).

Statistical analysis

Statistical analysis was performed with R software (version 3.4.3, R foundation, Vienna, Wien, Austria) and related packages including geepack and emmeans. Generalized estimating equations were used to account for within-patient inter-eye correlations.

RESULTS

Patient characteristics

The 28 patients had seen a primary eye-care provider or neurologist before referral to the neuro-ophthalmology clinic, but they had not received a definitive diagnosis (Fig. 1). Twenty patients (71%, 14 males, age=11–50 years) were diagnosed as visual snow syndrome (Table 1). The eight excluded patients comprised one diagnosed with rod-cone dystrophy (Fig. 2), one with idiopathic intracranial hypertension (Fig. 3), two with peripheral retinal degeneration that caused photopsia without visual snow, one with typical migraine with scintillating scotoma, one with transient photopsia after refractive surgery, one with visual snow symptoms for less than 2 months, and one with no additional visual symptoms who therefore did not meet the diagnostic criteria of visual snow syndrome (Fig. 1). The median age at onset was 19 years (range, 9 years to 46 years) among the 18 patients (90%) who could remember their time of onset. Most patients experienced more than two

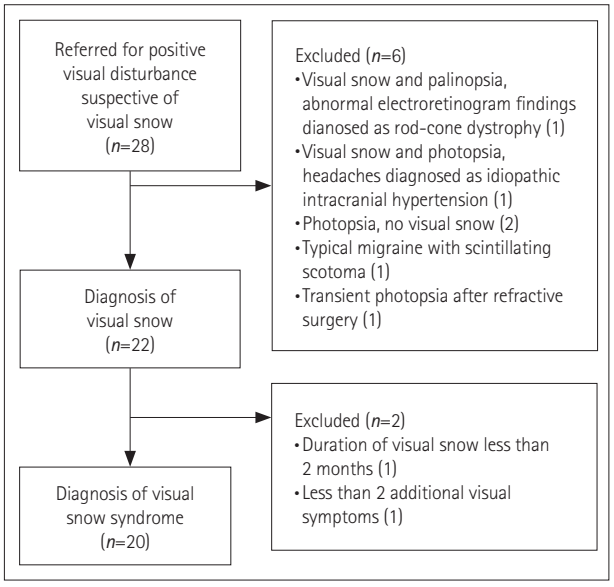

Fig. 1. Flowchart of the inclusion and exclusion of patients with visual snow syndrome.

Table 1. Demographics and clinical characteristics of patients with visual snow syndrome

Characteristic	Value
Demographics	
Age, years	25.4±10.4 (11–50)
Sex, male:female	14:6
Visual snow present since childhood	10 (2/20)
Age at onset, years	19 [9–46]
Symptom duration, years*	0.75 [0.25–20.00]
Continuous from first occurrence	94 (17/18)†
Progressive worsening	6 (1/18)†
Additional visual symptoms	
Palinopsia	61 (11/18)†
Floaters	71 (12/17)†
Blue-field entoptic phenomenon	65 (11/17)†
Spontaneous photopsia	53 (9/17)†
Photophobia	65 (11/17)†
Nyctalopia	44 (8/18)†
Additional nonvisual symptoms	
Tinnitus	78 (14/18)†
Concentration difficulty	47 (8/17)†
Phonophobia	53 (9/17)†
Lethargy	88 (15/17)†
Combined headache	60 (12/20)†
History of comorbid disease	
Migraine	56 (10/18)†
Typical migraine aura	11 (2/18)†
Anxiety	35 (6/17)†
Depression	35 (6/17)†

Data are mean±SD (range), *n*, % (*n*), or median [range] values.
*Symptom duration for patients who could recall, †Positive responses from patients who answered the questionnaire.

associated visual symptoms (Table 1).

Symptom progression could not be identified in 18 patients (90%). Associated nonvisual symptoms included concentration difficulty (47%), lethargy (88%), phonophobia (53%), and daily tinnitus (70%). Comorbid migraine was present in ten patients, which was without aura in eight of them. Six patients (35%) had depression and six (35%) had anxiety disorder. Panic disorder, posttraumatic stress disorder, and schizotypal personality disorder had been diagnosed in one patient each (Table 1).

Ocular examinations

Table 2 summarizes the ocular parameters of the patients diagnosed as visual snow syndrome.[4] BCVAs were less than 0.05 logMAR in both eyes for all patients, with normal findings for the color vision, visual field, and slit-lamp examination. Spherical equivalent refractive errors were less than -6.0 diopters in 18 of the 20 patients (37 eyes). The findings for the visual field (*n*=15), full-field ERG (*n*=12), and mfERG (*n*=12) were normal in all patients tested (Table 2).

Three patients showed exophoria of less than 20 prism diopters in primary gaze during both distance and near fixation. One patient who experienced traumatic visual loss in the left eye showed sensory esotropia. No patients complained of binocular diplopia or gaze limitation. Two out of seven patients in whom contrast sensitivity was tested had decreased contrast sensitivity in both distance and near fixation, including one with a history of migraine without aura. None of the patients with normal contrast sensitivity reported migraines or headaches related to visual snow (Table 2).

The pupil constriction ratio was below the normal range (<20%) in one patient who had comorbid migraine, depression, and anxiety disorder.[15] The average maximal pupil constriction velocity was 5.03±0.74 mm/s (mean±SD, *n*=14). The peripapillary RNFL thickness measured using SD-OCT (*n*=17) revealed no abnormalities, which was 95.9±7.8 μm in the global area and 77.2±12.5 μm in the temporal sector (Table 2).

Treatment outcome

Medication therapy was recommended, but most patients refused it because either their symptoms were tolerable, or they feared adverse events. The following medications were prescribed to five patients (25%): lamotrigine (25 mg/day) for one, propranolol (20 mg/day) for two, topiramate (25 mg/day) for one, and acetazolamide (750 mg/day) for one. Major adverse events of an allergic reaction and daytime sleepiness were found in one of the patients taking propranolol. None of the drugs resulted in symptom remission.

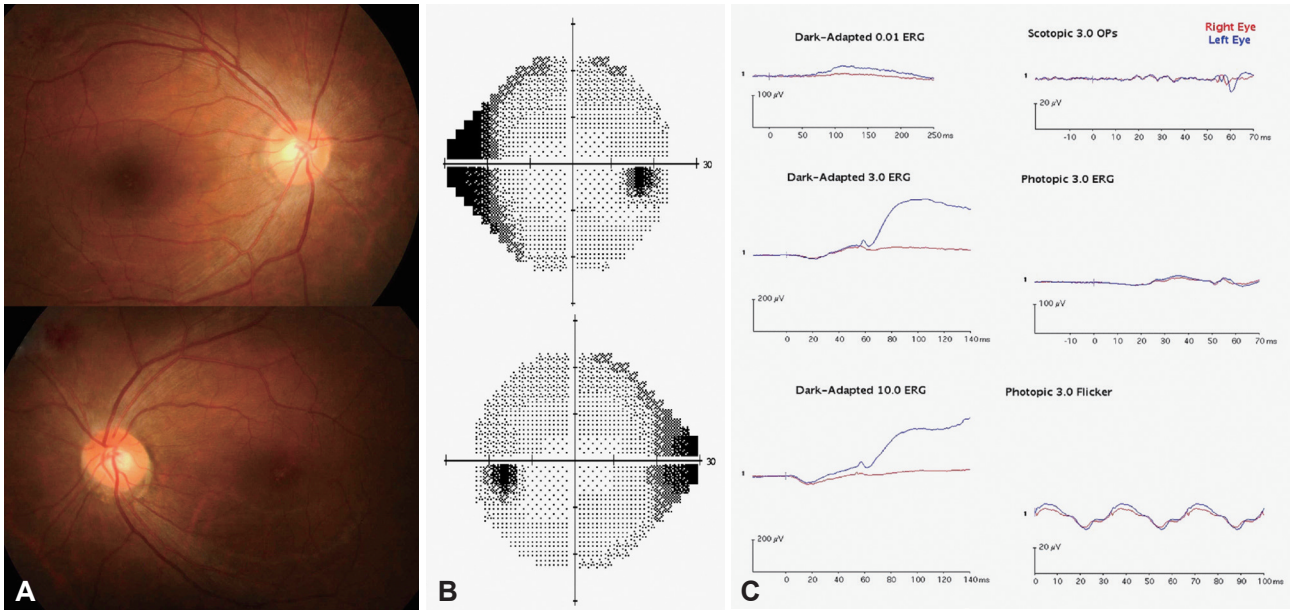

Fig. 2. Ocular findings of a patient with rod-cone dystrophy misdiagnosed as visual snow syndrome. A 36-year-old female presented with a 6-month history of nonprogressive visual snow that affected her entire visual field and could be relieved by wearing sunglasses. She reported palinopsia, enhanced entoptic phenomenon including excessive floaters, self-lighting of the eye, excessive blue-field entoptic phenomenon, nyctalopia, and photophobia. She suffered from migraine without visual aura. Her bilateral visual acuities were 20/20, and she had normal pupillary findings. A mild red-green color vision defect, diagnosed since childhood, was detected in both eyes by applying the Hardy-Rand-Rittler test. A: A fundus photography revealed normal appearances of the optic nerve head and retina. B: The Humphrey visual field test showed binasal visual field defects. C: On the full-field electroretinography, there was a severely diminished response to the dim white flash under scotopic conditions. The response to the bright flash under scotopic conditions was severely attenuated. Under light-adapted conditions (photopic single flash and 30-Hz flicker), the response was relatively preserved, indicating rod-cone dystrophy. There was no definite electrophysiological evidence of conduction defects in visual evoked potential. ERG: electroretinography, OPs: oscillatory potentials.

DISCUSSION

We evaluated the neuro-ophthalmologic findings in 20 patients with visual snow syndrome. Migraine, depression, anxiety, and tinnitus were highly prevalent comorbidities. The findings for the visual field, fundus examination, and RNFL thicknesses as measured using SD-OCT were normal. However, contrast sensitivity was impaired in two patients, one of whom suffered from migraine.

In line with other studies, patients experiencing visual snow reported continuous symptoms that mainly manifested in the second to fourth decades of life.[4,16] Our cohort was predominantly male (70%), in contrast with the female predominance[16] or sex neutrality reported previously.[4] Taken together with another report of male predominance,[3] these results support the concept that visual snow is not affected by sex.

The pupillary light reflex—including the constriction ratio, constriction latency, and maximal pupil constriction velocity—was evaluated in detail in this study. To the best of our knowledge, this is first study to examine pupillary light reflex parameters[15,17] measured with a digital pupilometer in patients with visual snow syndrome. Comparisons with the previously reported normal values of each parameter[15] revealed that the pupillary light reflex was intact in most patients. Meanwhile, an increased pupil constriction latency and a reduced redilation amplitude were reported in migraineurs with clinically severe symptoms,[17] while the pupil constriction ratio and constriction velocity were significantly decreased in patients with major depressive disorders.[18] The most likely neurobiological mechanism underlying these phenomena is an autonomic dysfunction that occurs in an anatomically intact system.[19] Visual snow shares some of the pathophysiological mechanisms of migraine aura. However, the alterations of sympathetic and parasympathetic functions found in chronic migraineurs have not been demonstrated in visual snow syndrome, and most patients in our cohort reported a relatively short symptom duration of less than 1 year. Therefore, further evaluations are needed in chronic patients with visual snow syndrome to determine if there is any change in the pupillary light reflex like there is in migraine.

Two patients exhibited decreased contrast sensitivity at all spatial frequencies compared with the normal reference values.[8] One patient with a contrast sensitivity deficit suffered from migraine without aura, while none of the patients with normal contrast sensitivity reported headaches or a history

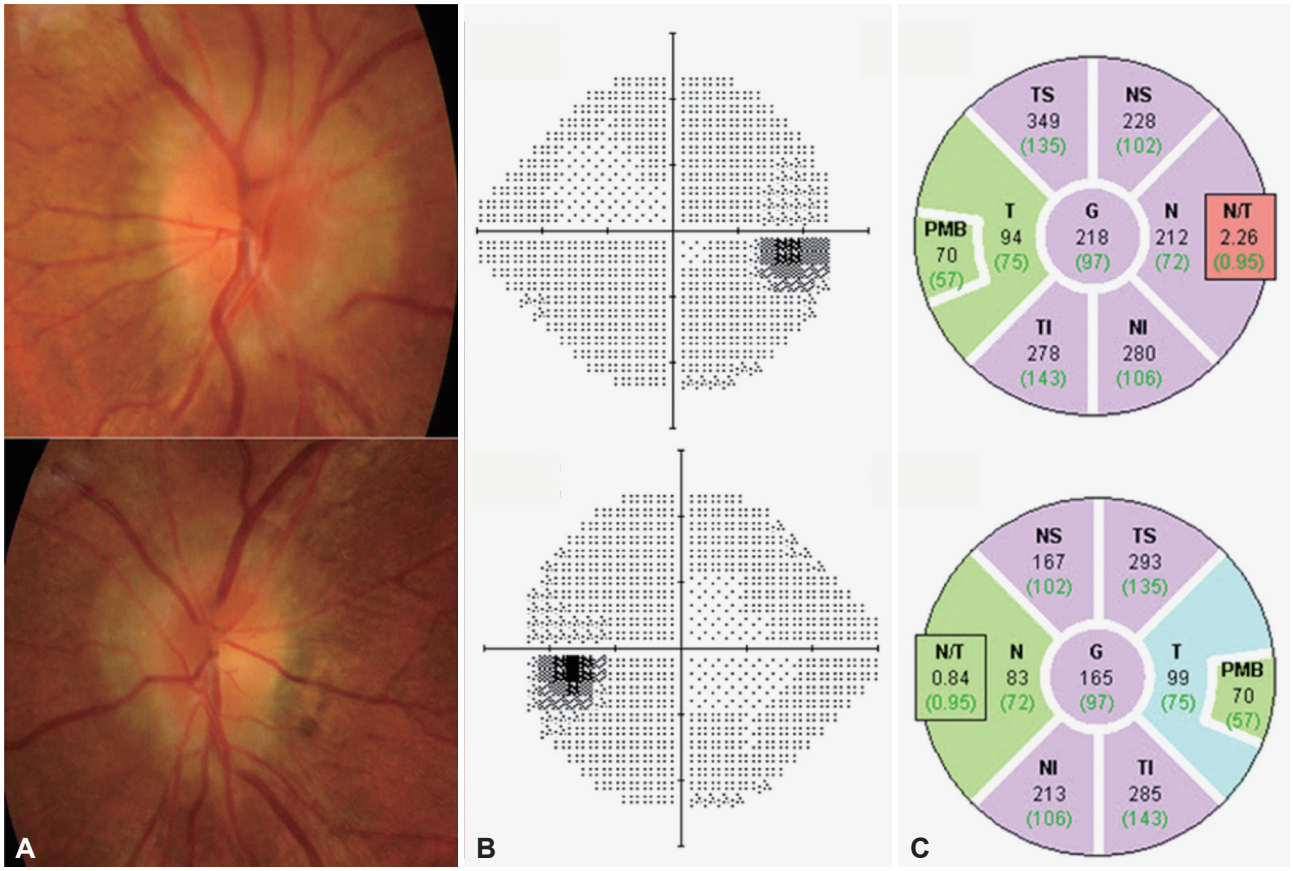

Fig. 3. Ocular findings of a patient with idiopathic intracranial hypertension misdiagnosed as visual snow syndrome. A 42-year-old male complained of visual snow that had first appeared 10 years previously, when silver spots had appeared in the entire visual field of both eyes, gradually increasing in size, and getting better after an hour of rest. Photopsia, entoptic phenomenon, and nyctalopia were noted. The patient had a long history of tinnitus, headaches diagnosed as migraine, and panic disorder. A: He had been diagnosed as having bilateral optic disc drusen due to mild optic nerve head edema, but normal vision. B: His visual acuity was 20/20 bilaterally, with normal findings for the pupillary light reflex, visual field testing, and full-field electroretinography. C: The circumpapillary thickness of the retinal nerve fiber layer measured using spectral-domain optical coherence tomography was increased in both eyes. A lumbar puncture revealed an opening pressure of 28.5 cm of water. Magnetic resonance venography demonstrated partial dural sinus thrombosis with sluggish flow. The carbonic anhydrase inhibitor acetazolamide (1 g/day) was prescribed, and the visual snow and photopsia resolved 3 weeks later. G: global, N: nasal, NI: nasal-inferior, NS: nasal-superior, N/T: nasal-temporal ratio, PMB: papillomacular bundle, T: temporal, TI: temporal-inferior, TS: temporal-superior.

of migraine. Contrast-sensitivity deficits have been reported previously in a cohort of chronic migraineurs.[8] The pathophysiological mechanism underlying the contrast-processing dysfunction in patients with visual snow syndrome is still unknown, and further investigations are needed on patients with chronic visual snow syndrome to better understand the relationship between visual snow syndrome and migraine.

Diagnoses of visual snow have been based on patient self-assessments, so efforts have been made to identify objective and quantitative tools for its assessment.[20,21] Yilidz et al.[20] demonstrated a loss of habituation response by repetitive-pattern-reversal visual evoked potentials in visual snow syndrome patients with and without migraine, which is thought to indicate occipital cortex hyperexcitability.[20] Visual-perception measures that have previously been used to investigate imbalance between the excitation and inhibition of the visual system in patients with other diseases were reported to be abnormal in patients with visual snow syndrome.[21] Specific biomarkers that can discriminate visual snow syndrome from other diseases are mandatory for identifying the characteristics and pathophysiology of this rare disorder.

Two of the patients referred from other clinics had underlying pathologies of rod-cone dystrophy and idiopathic intracranial hypertension. Since the additional visual symptoms included in the diagnostic criteria of visual snow syndrome can manifest in other visual disorders, it is important for clinicians to keep in mind the possibility of other diseases. Palinopsia is present in more than 80% of patients with visual snow syndrome,[4] but this condition can also be present in migraine patients with visual phenomena, focal brain lesions, and those taking preventive headache medications such as topiramate.[22] Photopsia and spontaneous light flashes can in-

Table 2. Ocular characteristics of patients with visual snow syndrome*†

Characteristic	Value
BCVA, logMAR	-0.06±0.07 (-0.18 to 0.05)
Refractive error, diopters	-2.14±2.76 (-9.25 to 2.00)
Presence of strabismus	20 (4/20)‡
Visual field testing	
Visual field mean deviation, dB	-0.52±1.86 (-3.00 to 3.58)
Visual field index, %	99.2±1.0 (96–100)
Pupil light reflex	
Constriction ratio, %	29.2±5.1 (17–38)
Latency, s	0.22±0.02 (0.19–0.25)
Maximum constriction velocity, mm/s	5.03±0.74 (3.49–6.47)
SD-OCT measurements	
Global RNFL thickness, μm	95.9±7.8 (83–110)
Temporal RNFL thickness, μm	77.2±12.5 (68–116)
Abnormal standard ERG	0 (0/12)‡
Abnormal mfERG	0 (0/12)‡
Reduced contrast sensitivity	28.6 (2/7)‡

Data are mean±SD (range) or % (*n*) values.
*Only 39 eyes of the 20 patients were included because 1 patient had unilateral traumatic optic neuropathy, †A generalized estimating equation was used for values accounting for intereye correlations. Both eyes were included in the analyses, ‡Abnormal findings in patients who received ocular examinations.
BCVA: best corrected visual acuity, ERG: electroretinography, logMAR: logarithm of the minimum angle of resolution, mfERG: multifocal electroretinography, RNFL: retinal nerve fiber layer, SD-OCT: spectral-domain optical coherence tomography.

dicate retinal or vitreal detachment, retinal degeneration, or cancer-associated retinopathy.[23] Photophobia is very common in migraine.[24] Finally, common causes of nyctalopia include retinitis pigmentosa[25] and vitamin A deficiency.[26] Therefore, a thorough ophthalmic examination including visual field testing, dilated fundoscopy, and ERG is crucial to avoid misdiagnosis.

Five of our patients were treated with medications and failed to obtain complete remission. The diagnostic criteria of visual snow were proposed only 5 years ago,[4] and there is still no consensus on its optimal treatment, with most of the available information on the effectiveness of treatment being based on case reports and clinical expertise.[27,28] Previous pharmacological treatments of visual snow and persistent visual phenomena have included diuretics,[28,29] anticonvulsants,[11,28] calcium-channel blockers,[2] beta blockers,[30] nonsteroidal anti-inflammatory medications,[2] antiplatelet agents, and antidepressants. In particular, the anticonvulsant lamotrigine, the diuretic acetazolamide, and the calcium-channel blocker verapamil are recommended as first-line therapies for visual snow.[7] Lamotrigine down-regulates glutamate, which is known to propagate cortical spreading depression in migraine.[31] van Dongen et al.[11] prescribed lamotrigine to 26 of 58 patients with visual snow syndrome, which led to partial remission in 5/26 (19.2%). However, their results provide little information since the proportion of comorbidities was not matched among treatments.

Since many patients with visual snow syndrome are reluctant to take medications due to concerns about adverse effects, nonpharmacological treatment may be suggested as an alternative option. Blocking the greater occipital nerve and using colorimetric lenses have been attempted,[32] and the National Hospital of Neurology in Sydney reported symptom improvements when using blue and yellow filters.[27] It is particularly interesting that a blue light can play a role in eliminating low-frequency brain rhythms by activating the koniocellular pathway.[3]

This study performed thorough ophthalmic and neurological examinations of 20 patients with visual snow syndrome. Most of the findings of the ophthalmic examinations including ERG, pupillary light reflex, and SD-OCT measurements were normal. Visual snow can be the chief complaint of an underlying retinal or neurological disease, and so a thorough ophthalmic examination including electrophysiological testing is necessary before making a diagnosis of visual snow syndrome.

Author Contributions

Conceptualization: Jeong-Min Hwang, Ji-Soo Kim. Data curation: Yung-ju Yoo, Hee Kyung Yang, Jeong-Yoon Choi. Formal analysis: Yung-ju Yoo, Hee Kyung Yang. Supervision: Jeong-Min Hwang, Ji-Soo Kim. Writing—original draft: Yung-ju Yoo, Hee Kyung Yang. Writing—review & editing: Jeong-Yoon Choi, Jeong-Min Hwang, Ji-Soo Kim.

ORCID iDs

Yung-ju Yoo https://orcid.org/0000-0001-8045-0391
Hee Kyung Yang https://orcid.org/0000-0002-1140-6036
Jeong-Yoon Choi https://orcid.org/0000-0003-2159-9967
Ji-Soo Kim https://orcid.org/0000-0002-1508-2024
Jeong-Min Hwang https://orcid.org/0000-0003-0837-2864

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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