Migraine biochemistry and visual snow

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Treatment effects and comorbid diseases in 58 patients with visual snow

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Abstract

Objective

To evaluate pharmacologic treatment options for visual snow and to report prevalence of comorbid diseases.

Methods

Medical charts of patients with a diagnosis of visual snow at the neurology outpatient clinic were reviewed on prescribed medication, and comorbid migraine, tinnitus, and psychiatric conditions including depression and anxiety.

Results

From 2007 to 2018, 58 patients were diagnosed with visual snow. Comorbid migraine was present in 51.7% of patients, lifetime depression in 41.4%, and lifetime anxiety in 44.8%. Lamotrigine was prescribed most frequently (26/58) and resulted in partial remission of symptoms in 5/26 (19.2%). No patients reported complete remission. Adverse events occurred in 13/26 (50.0%) patients. None of the other prescribed drugs (valproate [n = 7], topiramate [n = 4], acetazolamide [n = 2], flunarizine [n = 1]) led to improvement except for topiramate in one patient, who discontinued, however, because of adverse events.

Conclusions

Of medication prescribed (lamotrigine, valproate, acetazolamide, flunarizine), only lamotrigine afforded some improvement in a small minority of patients. Migraine, depression, anxiety, and tinnitus were common comorbid diseases.

Classification of evidence

This study provides Class IV evidence that for some patients with visual snow, lamotrigine resulted in partial remission of symptoms.

Introduction

Visual snow is characterized by the continuous presence of countless, small, flickering dots in the entire visual field.[1] Patients often describe it as seeing 'tv static', i.e. the noise of a detuned analogue television. Diagnosis of visual snow is made after exclusion of secondary causes of pan-field visual disturbances, such as lesions in the visual pathway, retinal pathology and occipital epilepsy. Visual snow *syndrome* is diagnosed in patients who in addition have ≥ 2 of the following visual symptoms: palinopsia, enhanced entoptic phenomena, photophobia or nyctalopia.[1] The pathophysiology of visual snow is unknown.[2] In the past visual snow was often believed to be a migraine phenomenon, because many patients also had migraine with aura.[1,3] However, in visual snow classical migraine characteristics such as (scintillating) scotoma or zig-zag lines are absent. Moreover, visual snow may also occur in patients without migraine.

Other diseases as tinnitus, depression and anxiety have also been frequently reported in patients with visual snow [1,3], but never been studied in an outpatient clinic setting.

Pharmacological treatment of visual snow is based on expert opinion and single case reports.[2,4,5] In one patient 50mg lamotrigine b.i.d. resulted in complete remission of visual snow.[4] More extensive evaluations of the effects of treatment in visual snow are not available.

In the present study we evaluated treatment responses in 58 patients with visual snow from our outpatient clinic and studied the comorbid diseases, notably migraine, tinnitus, depression and anxiety disorder.

Methods

We evaluated pharmacological treatment options and comorbidities in a case series of visual snow patients (Class IV evidence). Patients who were referred to our Neurology outpatient clinic with 'positive visual disturbances', between November 2007 and June 2018, were retrospectively included. Diagnosis of visual snow was made according to criteria as proposed earlier[1]. If patients had ≥2 additional visual symptoms they also met visual snow syndrome criteria.[1] Medical charts and referral letters were reviewed and data were extracted on demographics, comorbid migraine, medical history, performed diagnostic tests and prescribed medication. Depression and anxiety were evaluated as part of standard clinical care using a previously published mood disorder questionnaire and algorithm with validated cut-off scores for the Hospital Anxiety and Depression Scale (HADS) and the Center for Epidemiologic Studies Depression Scale (CES-D).[6] This

is standard for headache patients who visit our clinic, because of the shared comorbidity between migraine and mood disorders.[6] Since most visual snow patients were scheduled in headache consulting hours, they also received the questionnaire. Patients filled in the questionnaire before their visit. Lifetime depression was defined as HADS-depression score ≥8, or CES-D score ≥16, or (past) depression diagnosed by a physician, or (past) use of antidepressants for depression. Lifetime anxiety was defined as HADS-anxiety score ≥8, or (past) therapy for anxiety disorder, or (past) use of antidepressant for anxiety disorder.[6] Current depression was defined as HADS-depression score ≥8, or CES-D ≥16, and current anxiety was defined as HADS-anxiety score ≥8.[6]

For prescribed medication, dosage, adverse events and decision to continue or discontinue were documented. Complete remission was defined as absence of visual snow. Partial remission was defined as self-assessed reduction in symptom severity without a strict cut-off in minimum reduction because there is no standardized questionnaire for severity of visual snow.

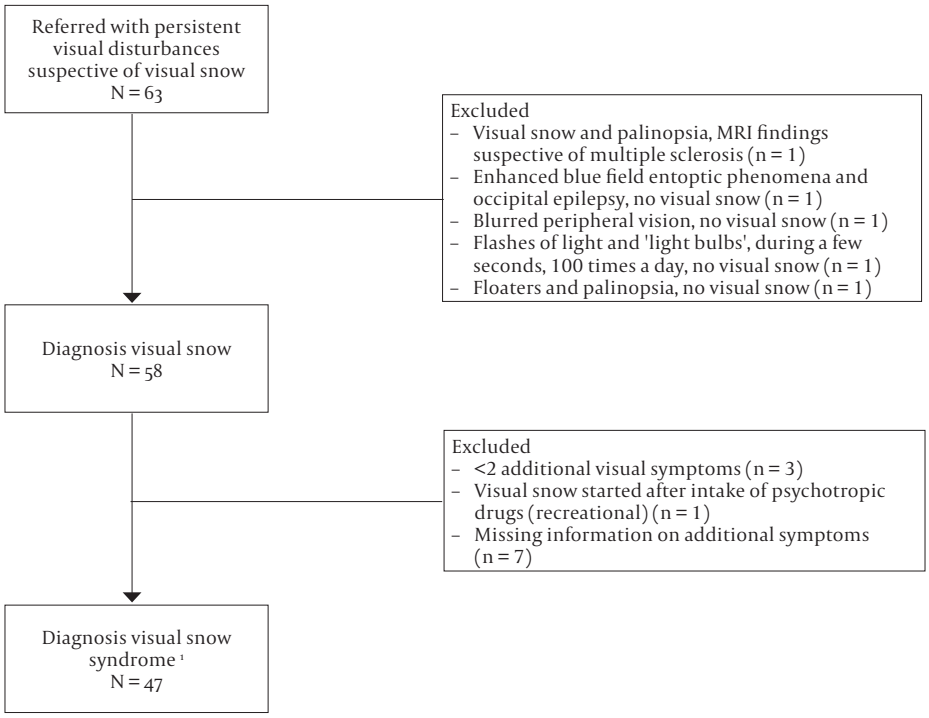
Standard Protocol Approvals, Registrations, and Patient Consents
This study was approved by the ethical committee of the Leiden University Medical Centre.

Data availability
Anonymized data can be obtained by request from any qualified investigator for purposes of replicating procedures and results.

Results

Of 63 referrals, 58 (92.1%) patients (29 females, 29 males) were diagnosed with visual snow and 47 (74.6%) additionally met visual snow syndrome criteria[1] (Figure 1). Some patients had self-diagnosed themselves and had explicitly asked their general practitioner for a referral. Clinical characteristics are summarized in Table 1. Median age of onset was 24.5 years (range 6-45) for patients who could remember onset of visual snow (48/58 patients). Comorbid migraine was present in 30 patients (51.7%), mainly migraine with aura (27/30). Six patients reported that visual snow started in close temporal association with a migraine with aura attack, in three during the attack and in another three in the few days thereafter. One patient reported onset of visual snow following a migraine without aura attack. Attack frequency in these seven patients was low (median 0.5 attacks/month, range 0.1 - 1.0) making a coincidental temporal association less likely.

Figure 1. Flowchart of study participants.



Legend: [1] Visual snow syndrome criteria as proposed by Schankin et al.

Lifetime depression was present in 24/58 (41.4%) patients and anxiety disorder in 26/58 (44.8%) (Table 1). Of the 36 patients who filled in the mood disorder questionnaire, current depression was present in 21 (58.3%) and current anxiety in 18 (50.0%). Prevalence of lifetime depression and anxiety was not correlated with the presence of comorbid migraine (both 50.0% in patients without migraine and 33.0% and 40.0% , respectively in patients with migraine). Daily tinnitus was present in 26/50 (52.0%) patients, absent in 24/50 (48.0%) and unknown in eight patients.

Table 1. Characteristics of n= 58 visual snow patients.

Demographics	
Age in years, mean (±SD)	29.7 (±10.2)
Female, n (%)	29/58 (50.0%)
Visual snow "as long as patient can remember", n (%)	10/58 (17.2%)
Visual snow onset later in life, n (%)	48/58 (82.8%)
Age of onset in years, median (range)	24.5 (6-45)
Visual snow started episodic, n (%) *	2/58 (3.4%)
Smoking	
Active smoker, n (%)	5/58 (8.6%)
Past smoker, n (%)	6/58 (10.3%)
Alcohol, current, n (%)	41/52 (78.8%)
Regularly, n (%)	25/52 (44.6%)
Units/week, median (IQR)	4.3 (1.3-10.0)
Infrequent, n (%)	19/52 (36.5%)
Recreational drug use, lifetime, n (%)	17/48 (35.4%)
Comorbid migraine	
Migraine, n (%)	30/58 (51.7%)
Migraine with aura, n (%)	27/58 (46.6%)
Migraine without aura, n (%)	3/58 (5.2%)
Attack frequency, median attacks/month (range)	0.25 (0-5)
Migraine attack in week before onset of visual snow, n (%) *	7/58 (12.1%)
Psychiatric comorbidities	
Depression, lifetime, n (%)	24/58 (41.4%)
Depression, current, n (%) [a]	21/36 (58.3%)
Anxiety disorder, lifetime, n (%)	26/58 (44.8%)
Anxiety disorder, current, n (%) [a]	18/36 (50.0%)
Depression and anxiety, lifetime, n (%)	16/58 (27.6%)
Depression and anxiety, current, n (%) [a]	13/36 (36.1%)
Derealisation/depersonalization feelings, n (%) *	9/58 (15.5%)
Other comorbidities	
Tinnitus, n (%) [c]	26/50 (52.0%)
Ophthalmological comorbidity not explaining visual snow, n (%) [d]	8/58 (13.8%)
Unexplained somatic conditions in medical history, n (%) [b]	9/58 (15.5%)

Legend: If denominator is smaller than n=58 this indicates missing data. * Spontaneously reported; this item was not routinely documented by physicians. [a] N=36 patients received the depression and anxiety questionnaire as part of standard clinical care, for remaining patients this was not yet routine procedure when they were referred. [b] I.e. irritable bowel syndrome, chronic fatigue syndrome, globus sensation in the throat. [c] Patient reported complaints of daily tinnitus. [d] All ophthalmological diagnoses were not explanatory for visual snow according to diagnosing ophthalmologist (correspondence available in n=47). Diagnosed before visual snow onset: retinal detachment OD, choroideremia ODS, macular degeneration OD, pseudoxanthoma elasticum ODS. Diagnosed after onset: acute glaucoma ODS, optic disc drusen ODS. Temporal relationship unknown: herpes zoster infection n. opthalmicus. OD = oculus dexter, OS = oculus sinister, ODS = both eyes.

Table 2 summarizes the various treatments and treatment responses. Lamotrigine was prescribed most frequently and resulted in partial remission of symptoms in 5/26 (19.2%) of patients; zero patients reported complete remission. Patients with partial remission reported "50% less intensity of visual snow" (n=1), "substantial reduction in intensity" (n=1) and "minor improvement in intensity" (n=3). Adverse events occurred in 13/26 (50.0%) of patients. Major adverse events were found in 4/13 patients (n=3 allergic reactions, n=1 excessive daytime sleepiness), leading to discontinuation within one month. All other adverse events were minor and these patients used lamotrigine for at least one month. Characteristics of patients who reported partial remission on lamotrigine ('responders') are described in Table 3. None of the other drugs (valproate, topiramate, acetazolamide and flunarizine) resulted in improvement of symptoms except for topiramate in one patient who discontinued, however, because of adverse events.

Table 2. Medication prescribed for visual snow.

Medication	**Treated**	**Adverse**	**Remission**		**Discontinued**	**Continued**
Target dose	(N) [a]	**events**	Partial [b]	Complete		
Lamotrigine 2x50mg [c]	26	13/26 (50%)	5/26 (19%)	0/26 (0%)	22/26 (85%)	4/26 (15%)
Valproate 3x300mg	7	5/6 (83%) [d]	0/7 (0%)	0/4 (0%)	7/7 (100%)	0/7 (0%)
Topiramate 2x50mg	4	4/4 (100%)	1/4 (25%)	0/4 (0%)	4/4 (100%)	0/4 (0%)
Acetazolamide 2x250mg	2	1/2 (50%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	0/2 (0%)
Flunarizine 2x5mg	1	1/1 (100%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)

Legend: [a] Majority of patients initiated treatment at our center except for n=6 lamotrigine, n= 3 valproate, n= 1 topiramate case and n=1 acetazolamide cases where referring physician had already prescribed medication. Regarding lamotrigine: in 2/6 cases the referring physician had stopped lamotrigine because of adverse events, in 2/6 cases the referring physician had stopped lamotrigine after sufficient dosage (at least 2x50mg for at least 3 months) because it did not improve symptoms, in 2/6 cases the lamotrigine was stopped at the LUMC clinic because there was no improvement of symptoms after sufficient dosage. Regarding valproate, topiramate and acetazolamide: the referring physician had already stopped medication because of adverse events. [b] Patient reported reduced intensity of visual snow but symptoms did not completely disappear. [c] 2x50mg is the minimum that was targeted. Out of the nine lamotrigine users without adverse events and without improvement in symptoms, 5/9 received at least 2x100mg (one case for at least one month, four other cases for at least four months) and 4/9 received 2x50mg for at least two months. Responders already reported improvement of symptoms at 2x50mg. Dose was further increased in one responder to 2x100mg with additional improvement in symptoms and in one responder to 1x100mg+1x50mg with no further improvement. [d] For one patient on valproate it was not documented whether adverse events occurred.

Table 3. Characteristics of lamotrigine responders versus non-responders.

	Responders (n=5)	Non-responders (n=14)
Female, n (%)	3/5 (60%)	3/14 (21%)
Age at presentation in years, median (range)	29 (23-46)	30 (18-45)
Age of onset in years, median (range)	28 (15-45)	29 (16-45)
Visual snow as long as patient can remember, n (%)	0/5 (0%)	2/14 (14%)
Comorbid migraine, n (%)	4/5 (80%)	6/14 (43%)
Migraine with aura, n (%)	3/5 (50%)	5/14 (36%)
Comorbid depression, lifetime, n (%)	2/5 (40%)	7/14 (50%)
Comorbid anxiety disorder, lifetime, n (%)	1/5 (20%)	8/14 (57%)

Legend: Responders: patients with partial remission (defined as self-assessed reduction in symptom severity without a strict cut-off in minimum reduction). Non-responders: patients using lamotrigine for at least two months at a dosage of at least 50mg b.i.d. and with no improvement in symptoms; i.e. patients who did not reach this dosage because of adverse events were excluded from this analysis.

None of the other drugs (valproate, topiramate, acetazolamide and flunarizine) resulted in improvement of symptoms except for topiramate in one patient who discontinued, however, because of adverse events. Twenty-nine patients did not want to start therapy as no evidence-based therapies could be offered or because of fear for adverse events. It cannot be excluded that symptoms were less severe in these patients.

Discussion

We evaluated treatment response and comorbid diseases in 58 patients with visual snow. Lamotrigine was prescribed most frequently and resulted in partial remission in 5/26 patients. No treatment resulted in complete remission of symptoms. Migraine, depression, anxiety and tinnitus were highly prevalent comorbid disorders.

Information on treatment of visual snow is limited to case reports. Lamotrigine 50mg b.i.d. was effective in one case (complete remission)[4], but not in two other cases.[5] In our patients lamotrigine afforded partial remission in 5/26 (19%) patients. A randomized controlled trial is needed to better determine the efficacy of lamotrigine, preferably using a minimum dosage of 100mg b.i.d.. Nonetheless, we believe the present data indicate there will be a large group of patients who will not benefit from lamotrigine. Future research on novel treatment options is necessary, including other approaches such as neuromodulation. The numbers for the other drugs are too small to determine efficacy, however, we consider their adverse events profiles less favorable than lamotrigine.

In line with other studies migraine was more prevalent than in epidemiological studies in the general population, in particular migraine with aura. It has therefore

been hypothesized that both migraine aura and visual snow share pathophysiological mechanisms and are a consequence of cortical hyperexcitability.[7] Indeed, in some patients visual snow had started during or shortly after migraine aura which might support this hypothesis.

Since many patients also had depression and anxiety, we advise to screen patients with visual snow for these conditions. In our study population ≥50% of patients had active depression or anxiety symptomatology, which is higher than in earlier studies. One study found depression in 11/78 (14.1%) patients and anxiety in 12/78 (15.4%) patients, using the PHQ-8 and GAD-7 questionnaire. However, patients were recruited via social media and may differ from those seeking help from a doctor.[1] In a neuro-ophthalmology clinic, 6/32 (19%) patients had depression and 14/32 (44%) patients anxiety disorder, but only medical charts were reviewed for past diagnoses.[3]

The current study cannot provide an answer on whether there is a causal relationship between these comorbidities. Depression/anxiety may either be cause or consequence of visual snow, or might share underlying (genetic) risk factors as is the case for the bidirectional relationship between depression and migraine.[8,9] We advise to treat depression and anxiety in visual snow patients because these might negatively impact disease burden and coping behavior. For tinnitus it is known that depression is associated with higher disease burden[10] and comorbid depression in migraine patients increases the risk of medication overuse and migraine chronification.[11] Furthermore, cognitive therapy is effective in reducing tinnitus severity and impairment.[12] Cognitive therapy might therefore be effective in visual snow as well.

The strength of this study is the relatively large number of patients seen at a Neurology clinic. There are, however, limitations. The retrospective design might have caused selection-, recall- and information bias. Additional visual symptoms were not documented for all patients since the criteria for visual snow syndrome were only published in 2014.[1,13] Nonetheless, all our patients had the diagnostic symptom of visual snow. Depression/anxiety questionnaire data were only available for 36/58 (62.1%) patients. Evaluation of treatment was based on medical charts rather than a standardized protocol. However, this did not change the observation that the vast majority of patients stopped therapy. Patients were referred to a headache centre which could have led to selection of cases with comorbid migraine. However, patients were not referred for their migraines but for 'persistent visual complaints'.

Migraine, depression, anxiety and tinnitus are prevalent in visual snow. Different treatments were prescribed for visual snow, but all failed except for some improvement in a small minority of patients using lamotrigine.

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