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## **Prevalence and mimics of Kleine-Levin Syndrome: A survey in French-speaking Switzerland**

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## **Abstract**

### **Introduction**

Kleine-Levin syndrome (KLS) is a rare disease of unknown aetiology, whose diagnosis may be challenging. We aimed to estimate KLS prevalence in French-speaking Switzerland, and assess differences with mimicking conditions.

### **Methods**

In this population-based approach, we contacted Swiss sleep-certified centers and neurologists in French-speaking Switzerland, and gathered detailed clinical data from patients referred for recurrent hypersomnia or suspected KLS.

### **Results**

We identified 7 patients with diagnosed KLS (6 since 2009), leading to a prevalence estimation of 3.19 per million (95% confidence interval: 1.55-6.59). Median age at diagnosis was 17 years (range; 12 - 19), 71.4% of them were men and mean diagnosis delay after the first episode was  $20.1 \pm 10.9$  months. We identified 9 mimics patients referred to our center; they differed from KLS patients by their higher age at disease onset (median: 15 (range; 12-16) vs 19 (range; 16-64) years;  $p < 0.001$ ), suspected KLS as referral reason (more frequent in mimics,  $P = 0.003$ ), and precipitant factors (more frequent in KLS,  $P = 0.011$ ). Of the mimics patients, 77% (versus 28% in KLS) had a psychiatric diagnosis.

### **Interpretation**

This study suggests a relatively higher KLS prevalence than previously reported. As compared to KLS, mimics patients have higher age at symptoms onset, they are more often referred for KLS suspicion, and have a higher prevalence of psychiatric disorders.

**Keywords:** Comorbidities, KLS mimics, recurrent hypersomnia, sleep, sleepiness

### **Introduction**

Kleine-Levin syndrome (KLS) is a rare disease characterized by a minimum of two recurrent episodes of hypersomnia, lasting from 2 days to 5 weeks, which recur at least once every 18 months, and are accompanied by at least one of the following symptoms: cognitive abnormalities, altered perception, eating disorder (hyperphagia or anorexia) and disinhibited behaviour such as hypersexuality. Between episodes, alertness, behaviour and cognitive functions usually become normal.<sup>1</sup> Diagnosis requires the exclusion of other disorders, mainly psychiatric (such as bipolar psychosis) or sleep related (such as idiopathic hypersomnia or narcolepsy). Its diagnosis may be very challenging, as no recognized biological marker has been identified.

KLS occurs mainly in young male adolescents and may wear off in adulthood.<sup>2</sup> Its pathophysiology is still unknown, although according to recent functional-imaging-studies; hypothalamus, thalamus, caudate nucleus, angular gyrus, anterior cingulate, dorsomedial prefrontal, orbitofrontal and temporal cortices seem to be hypoperfused during episodes.<sup>3-8</sup> Several precipitant factors have been described before occurrence of an episode, among which infections, followed by alcohol consumption, sleep deprivation, unusual stress and head trauma.<sup>2,9-12</sup> A study pointed to a significantly increased HLA-DQB1\*0201 allele frequency in KLS patients, leading to a possible autoimmune hypothesis, but this has not been confirmed in larger cohort.<sup>2,13</sup> Actually no placebo-controlled trials concerning treatment management are available, although lithium seems to be the most widely assessed prophylactic drug for patients with frequent and disabling episodes.<sup>2,12,14,15</sup>

The prevalence of KLS, classically given at 1 per million, has been recently evaluated at 1.8 cases per million in France.<sup>9</sup> At our center, we currently follow several KLS patients, suggesting a somewhat higher prevalence than described in the literature. Moreover, we also ruled out KLS diagnosis in a consistent number of patients in recent years referred for this suspicion.

The aim of our study was thus to estimate the prevalence of KLS in the French-speaking part of Switzerland, and to characterize the typical clinical presentation of these patients, with the purpose to compare it with the presentation of patients with mimicking diagnoses, among which KLS was first suspected but finally ruled out.

## **Methods**

### *Design and Subjects*

Data from all patients referred to our center for recurrent episodes of hypersomnia or suspected KLS, identified by AOR and JHR, were retrospectively reviewed between November 2006 and August 2015. Additionally, all private-practice neurologists and sleep-specialists working in certified sleep-centers of the French-speaking part of Switzerland, including the Cantons of Vaud, Neuchâtel, Jura, Geneva, Fribourg, Valais (French-speaking districts), and Bern (French-speaking districts and Bern-city), were asked if KLS patients from the French-speaking side of the country were diagnosed and/or followed. The Vaud Cantonal Ethics Committee on research involving humans approved the study.

### *Data collection*

For patients fulfilling the KLS criteria of the International Classification of Sleep Disorders,<sup>1</sup> we collected data concerning: Demographics, time of first episode, time of diagnosis, number and duration of episodes, interval between episodes and since the last relapse, pharmacological treatment, precipitant factors, and disease evolution (relapsing remitting vs long episodes). We indexed the first symptoms of the disease and the referral reason, the presence of hypersomnia (at least in two episodes), cognitive, eating, sexuality-related disorders, behavioural or psychological disturbances. We also collected the therapy currently used and the presence of comorbidities. For patients referred for suspected KLS but for which this diagnosis was not confirmed (“mimics”), we collected the following data: Demographics, final diagnosis, precipitant factors, first symptoms of the disease, referral reason, the presence of cognitive, eating, sexually-related, behavioural or psychological disturbances, and the presence of comorbidities. When available, we also reviewed data from complementary investigations, including brain MRI, PET-CT, standard EEG, polysomnographic recordings, MSLT, actigraphy, biological measures, lumbar punctures, CSF examination, urine tests and Neuropsychological investigations.

### *Statistical analysis*

Comparisons between groups were performed using Mann-Whitney *U* tests or two-tailed Fisher’s exact tests, as needed. The prevalence was calculated (using the Wilson’s method for the confidence interval, in view of the low numbers), using the data provided by the Swiss Federal Statistics Office (Federal Statistical Office, Neuchâtel 2015, accessed on September 28<sup>th</sup> 2015).<sup>16</sup> The number of inhabitants in 2014 (in parentheses) of the Cantons of Fribourg

(303.337), Geneva (477.385), Jura (72.410), Neuchâtel (177.327), and Vaud (761.446) were included. Concerning the Bern and Valais cantons, only the French-speaking districts were considered: Jura-bernois and Biel (151.246) regarding Bern, and Conthey, Entremont, Hérens, Martigny, Monthey, Saint-Maurice, Sierre and Sion (249.479) regarding Valais. The total number of inhabitants used to calculate the prevalence in the French-speaking Switzerland was 2'192'670. We did not correct for multiple comparisons, given the exploratory character of this study. Comparisons between prevalence of KLS in French-speaking Switzerland and France were assessed using a likelihood ratio  $\chi^2$  test.

## Results

We identified 7 patients with KLS according to the ISCD-3 criteria,<sup>1</sup> and 9 mimic cases, whose details are summarized in **Table 1 and 2**. Apart from a patient formerly diagnosed in 2002, all other subjects were diagnosed since 2009.

### *Prevalence of KLS*

The estimated prevalence of KLS in the French-speaking part of Switzerland was 3.19 per million (95% confidence interval: 1.55-6.59); this was not statistically different from the 1.8 per million estimation in France (P=0.148).<sup>9</sup> **Figure 1** shows the geographical distribution of KLS patients; **Figure 2** compares the number of KLS patients to the inhabitants of each Swiss canton considered in this study. Five subjects were living in the canton of Vaud, and the remaining two in Fribourg and Valais.

### *KLS patients characteristics*

Six patients were diagnosed and followed-up at our center, four young men and two young women. One additional man was identified outside our hospital, in Valais. **Table 1** shows the clinical characteristics of KLS patients. Mean age at diagnosis was 17 years (range; 12 – 19), and median age at onset was 15 years (range; 12 – 16). The mean delay to diagnosis after the first episode was  $20.1 \pm 10.9$  months, the mean duration of the episodes was  $7.42 \pm 2.37$  days, with a median disease-free interval of 2 months (range ; 1 – 35). The reported precipitant factors were: influenza-like infection (in four patients), alcohol consumption (in two), and long-time video gaming (in one). Two young men presented an unfavourable course, with progressively frequent and longer episodes (in one patient, an episode lasted over one year), and shorter illness-free intervals. The five other patients experienced a typical relapsing-

remitting course. One subject was not taking any treatment, one ritaline and lamotrigine, and the other five were under lithium (two with additional compounds: escitalopram and amantadine in one each); an increase in duration of disease-free intervals were observed in three patients taking lithium. We observed one recurrence upon lithium weaning in one of them, and in two patients, lithium possibly helped to a remission (in association with amantadine in one of them). In one patient, lithium decreased subjectively the severity of the symptoms, and in another patient, lithium did not alleviate the symptoms. Psychiatric evaluation revealed that two of them had a psychiatric comorbidity, respectively depressive and anxiety disorder (**Table 2**). Extensive complementary investigations were normal or showed non-specific abnormalities, and did not enable specific distinction between KLS and mimics patients.

#### *Mimics patients and differences with KLS-patients*

Nine patients were detected at our center, four males and five females. Their median age at diagnosis was 26 years (range; 17 – 64), and the median age at symptomatology onset was 19 (range; 16 to 64). In 7/9 (77%) mimic patients, psychiatric diagnoses were retained, which are given in **Table 2**. The definite diagnoses in the two remaining mimic patients were idiopathic hypersomnia and a circadian sleep disorder.

**Table 2** highlights differences between KLS and mimics patients. Patients with well-defined KLS were referred for suspicion of viral encephalitis or epilepsy, feverish state unknown origin, mental slowness, and idiopathic hypersomnia, whereas the majority of mimics patients were referred for KLS suspicion. KLS patients had also a younger age than mimics patients regarding symptomatology onset. We found only one mimic patient who presented an influenza-like infection as precipitant factor. Two reported a psychological stress (sentimental rupture, family and work-related stress), the remaining 6 patients reported no specific precipitant factors, whereas all KLS patients presented one. Others clinical characteristics, including cognitive symptoms, eating-disorders, behavioural disturbances, sexual-related disorder, psychological symptoms, did not show any remarkable differences.

## **Discussion**

This study estimates the prevalence of KLS in the French-speaking part of Switzerland at 3.19 per million (95% CI: 1.55-6.59), and highlights the differences between defined KLS patients and mimics, who tended to be older at disease onset, with no major gender predominance and were mainly specifically referred to a specialized center for KLS suspicion. All KLS patients presented precipitant factors, while only 3 mimics patients reported one. Symptoms, including cognitive and psychological symptoms, eating and sexual-related disorders, and behavioral disturbances could be close, although mimics patients seem to present less derealisation, The definite diagnosis retained for mimics was a psychiatric disorder.

Our estimated prevalence of KLS seems somewhat higher than previously published data; 1.5 per million worldwide,<sup>14</sup> and 1.8 per million in France,<sup>9</sup> a difference that is not statistically significant as compared to France. The geographical distribution of KLS patients, and the marked overrepresentation of patients from the canton of Vaud (5 out of 7), may suggest that this entity could remain underdiagnosed in some areas with limited access to specialized centers. We might still have missed some KLS patients, despite contacting all certified sleep centers and neurologist in the study region; alternatively, a yet unidentified factor related to genetics or exposure could be at play; indeed, KLS prevalence strongly varies across French regions.<sup>9</sup>

The mean latency of diagnosis of the KLS patients in our study (20 month) appears relatively shorter than previously described; about 4 years in 2001,<sup>17</sup> and 2 years in 2011,<sup>11</sup> and indicates that increasing KLS awareness, at least in selected centers, may influence this aspect. Whether this tendency of higher prevalence as compared to the classically given prevalence at 1-1.5 per million reflects a natural fluctuation or is the consequence of increased awareness remains to be determined; the fact that in our study 6 out of 7 patients have been diagnosed after 2009 favors the second hypothesis.

The clinical presentation of KLS patients may be difficult to distinguish from mimics. Our study shows that mimics are mostly related to various psychiatric disorders. Marked differences between KLS patients and mimics cases were observed in the referral reasons: while KLS patients had a suspicion of viral encephalitis, epilepsy, mental slowness or hypersomnia, the majority of mimics patients were specifically referred for KLS suspicion. This underscores the need for patients with KLS suspicion to undergo a formal neurologic



and a psychiatric interview as pointed out recently.<sup>9</sup> KLS patients had also younger age at symptoms onset, a predominance of males, and the age at disease onset in our cohort is similar to previously reported cases.<sup>2,11,12,14</sup> This underlines the fact that KLS is predominantly an adolescent-onset disease, and adult-onset is much less frequently observed.<sup>12,14,18</sup> KLS and mimics patients also differed according to events associated with disease onset: all KLS patients reported precipitant factors, among them a majority of influenza-like infection, versus only 3 mimics patients. This significant difference should be viewed cautiously, since a minority of KLS patients reported in the literature did not remember precipitant events.<sup>2,14</sup> Finally, it is interesting to note that in our center mimic patients outnumbered KLS patients, as opposed to a recent French nationwide publication.<sup>9</sup> This may reflect a referral bias or a geographical specific characteristic, but may be of interest for practicing sleep specialists and neurologists.

All KLS patients described cognitive impairment, but none reported sexual-related disorders; a minority had ictal megaphagia, or appetite loss. This emphasizes the importance of the cognitive disorders, specifically derealisation, as one of the core symptoms of KLS, and that sexual-related disorders seem only inconstantly found.<sup>2,9-12</sup>

Concerning treatment, five KLS patients were currently taking lithium and all reported improvement, with longer disease-free interval in four. Two of them reported no more episodes, since respectively 40 and 11,5 months until August 2015. In one patient, a recurrence was observed upon progressive lithium weaning, and a favourable therapeutic response was obtained after lithium increase, as previously reported.<sup>2,12,14,15</sup> In two patients, an unfavourable course was observed: their episodes became more frequent and longer, merging into them with shorter illness-free intervals. This evolution course seems to be more frequent than previously described, also in the light of a recent study with a large cohort of KLS patients,<sup>9</sup> and challenges the idea that KLS is a “benign” disease.

To the best of our knowledge, this is the first population-based study assessing KLS prevalence not only in Switzerland, but outside France<sup>9</sup> (and besides one worldwide estimation from previously published cases<sup>14</sup>). The characterisation of clinical presentations and course of KLS provides clues to differentiate defined KLS patients and potentially mimics patients. However, we acknowledge potential limitations. Its retrospective design prevented an optimal data ascertainment in each patient, and the diagnostic workup was not

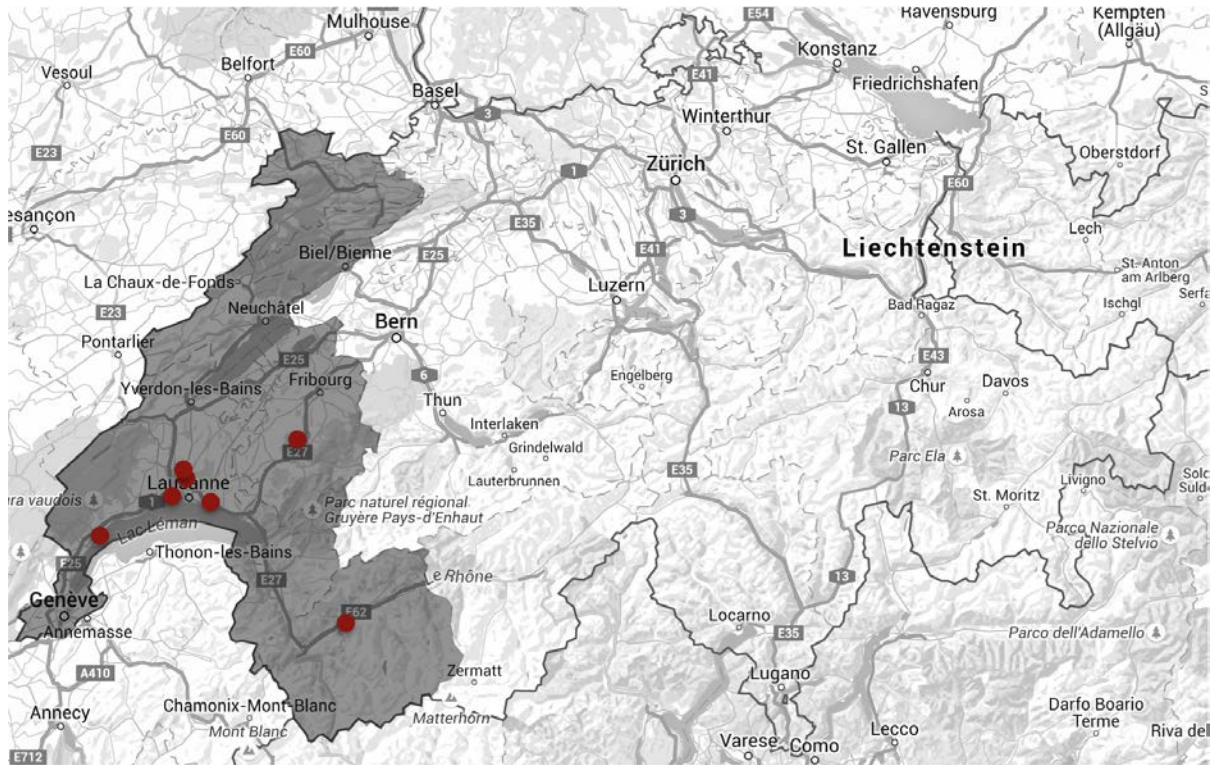
uniform. The sample size was also relatively small and we could not find many statistically significant differences. It is possible that not all the KLS patients in the French-speaking Switzerland could be identified despite our efforts. Finally, while we used a population-based approach regarding KLS patients, mimics patients were only recruited in our center.

### **Conflict of interests**

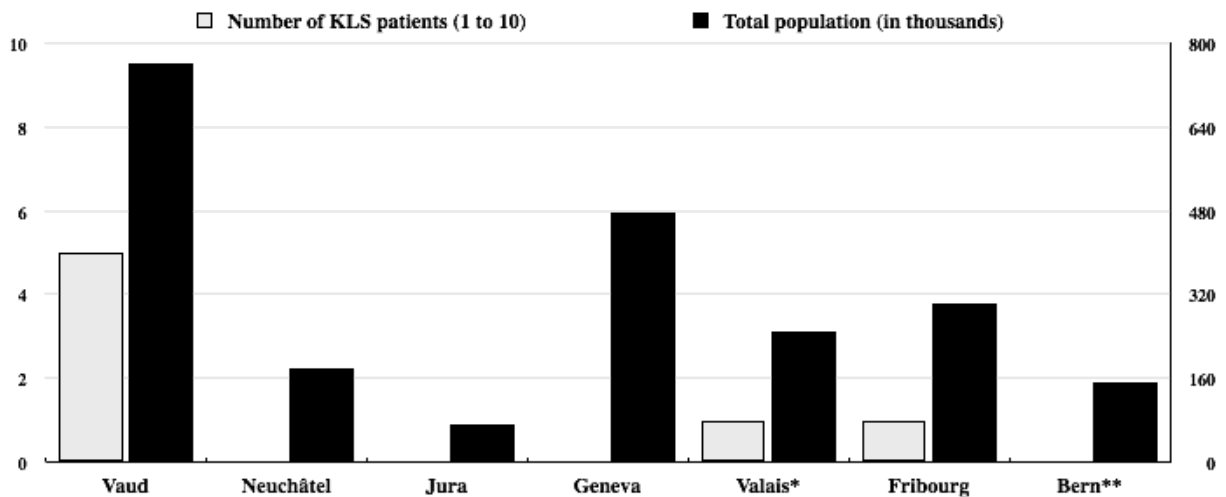
The authors declare that they have no conflict of interests.

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**FIGURE 1.** Geographical location of identified patients with Kleine-Levine syndrome (each point represent one patient); the darker coloration represents the French-speaking area of Switzerland. Map built with the help of © 2015 Geobasis-DE/BKG (©2009), Google, <https://www.google.ch/maps>.



**FIGURE 2.** Comparison between number of KLS patients (from 1 to 10, left axis, grey) reported in every considered canton and total population of these cantons (in thousands, right axis, black). \*Regarding the Canton of Valais, only the population currently living in the French-speaking districts was considered. \*\*Concerning the Canton of Bern, only the population currently living in the French-speaking districts was considered.

**Table 1. Clinical characteristics, therapy and comorbidities of KLS patients (n=7)**

Patient	Age	Gender	Delay to diagnosis (Months)	Number of episodes	Episodes duration (days)	Interval between episodes (months)	Precipitant factors (at minimum 1 episode)	Disease course	Therapy at 08.2015	Tried therapy	Improvement with therapy	Time since last episode (08.2015)	Comorbidities
1	24	M	4	>> 40	10	2	Influenza-like infection	fluctuating with chronicization	Lithium Escitalopram	Carbamazepine Valproic acid Acebutolol Melatonin Modafinil Lamotrigin Amantadin Zolpidem Venlafaxine	Increase disease-free interval	< 1 month	Depressive disorder
2	22	M	17	10	5-10	6-35	alcohol consumption	Relapsing-remitting	Lithium	Modafinil	Increase disease-free interval ; recurrence upon lithium weaning	3 months	Migraine without aura
3	22	F	30	5	10	12	alcohol consumption	Relapsing-remitting	Lithium	Modafinil	Possibly helps to a remission ; Undergoing lithium weaning	40 months	Anxiety disorder coeliac disease
4	22	M	37	>23	4-7	1.5	Longtime video-gaming	fluctuating with chronicization	Lithium	Amantadin Lamotrigin Modafinil Zolpidem	Subjective decrease severity of symptoms	Chronicization	None
5	19	M	21	14	3-4	6	Influenza-like infection	Relapsing-remitting	Lithium Amantadine	-	Increase disease-free interval and possibly helps to a remission	11,5 months	None
6	18	F	20	26	7	1	Influenza-like infection	Relapsing-remitting	Lamotrigin, Ritaline	Lithium Modafinil Zolpidem	None	< 1 month	None
7	17	M	12	10	7-10	1	Influenza-like infection	Relapsing-remitting	None	-	None	2 months	Acute lymphoblastic leukemia in childhood
Mean ± SD or Median with range			20.14 ± 10.95	10 (range ; 5 to 40)	7.42 ± 2.37	2 (range ;1 to 35)							

**Table 2. Comparison between Kleine-Levin and mimic patients, regarding clinical characteristics.**

	<b>KLS patients (n=7)</b>	<b>Mimics patients (n=9)</b>	<b>p value</b>
<b>Age at symptoms onset (range; years)</b>	15 (range ; 12 – 16)	19 (range ; 16 – 64)	<b>0.001</b>
<b>Male gender</b>	5/7 (71.42 %)	4/9 (44.5 %)	<b>0.35</b>
<b>Referral reason</b>	- 2 suspicion of viral encephalitis - 1 feverish state unknown origin - 1 epilepsy suspicion - 1 mental slowness - 2 idiopathic hypersomnia	- 7 KLS suspicion - 1 recurrent idiopathic hypersomnia - 1 sleep disorder in relation with increased work rhythm and heartache	<b>0.003</b> (for referral of suspected Kleine-Levin)
<b>Precipitant factors (at minimum 1 episode)</b>	7/7 (100%)	3/9 (33.4 %)	<b>0.011</b>
<b>Cognitive symptoms</b>	7/7 (100%)	8/9 (88.8 %)	1.000
Derealisation	6/7 (85.71 %)	3/9 (33.4 %)	
Attention/concentration deficits	6/7 (85.71 %)	6/9 (66.7 %)	
Memory deficits	3/7 (42.85 %)	5/9 (55.6 %)	
Amnesia	5/7 (71.42 %)	3/9 (33.4 %)	
<b>Eating disorders</b>	5/7 (71.42 %)	5/9 (55.6 %)	0.816
Megaphagia	3/7 (42.85 %)	4/9 (44.5 %)	
Decrease of appetite	2/7 (28.57 %)	1/9 (11.2 %)	
<b>Behavioral Disturbances</b>	4/7 (57.14%)	8/9 (88.8 %)	0.261
Regression	1/7 (14.28%)	1/9 (11.2 %)	
Inappropriate behavior	2/7 (28.57 %)	0	
Irritability	3/7 (42.85 %)	7/9 (77.8%)	
Impaired speech	1/7 (14.28%)	0	
<b>Sexual-related disorder</b>			
Hypersexuality	0	3/9 (33.4%)	0.213
<b>Psychological symptoms</b>	5/7 (71.42 %)	6/9 (66.7 %)	1.000
Psychomotor slowing-down	2/7 (28.57 %)	1/9 (11.2 %)	
Hypothymia	4/7 (57.14%)	4/9 (44.5 %)	
Anxiety	1/7 (14.28%)	5/9 (55.6 %)	
<b>Psychiatric comorbidities</b>	2/7 (28.57 %)	7/9 (77.8%)	0.126
Depressive disorders	1/7 (14.28%)	4/9 (44.5 %)	
Anxiety disorders	1/7 (14.28%)	2/9 (22.3%)	
Bipolar disorder	0	1/9 (11.2 %)	
Borderline disorder	0	1/9 (11.2 %)	
Mental anorexia	0	1/9 (11.2 %)	
OCD	0	1/9 (11.2 %)	

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