Kleine-Levin syndrome

Familial cases and comparison with sporadic cases

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ABSTRACT

الأهداف: لتسليط الضوء على ظهور المتلازمة في الحالات العائلية وتحديد ما إذا كان الطيف المرضي في الحالات العائلية من متلازمة كلاين– ليفن (KLS) مشابه لما يتم مشاهدته في الحالات العشوائية.

الطريقة: جمعت التقارير المتعلقة بحالات متلازمة كلاين– ليفن العائلية خلال الفترة من سبتمبر حتى ديسمبر 2014م من خلال البحث في مكتبة الكونجرس، و موقع (PubMed)، وقاعدة بيانات (Web of Science) مع حصر البحث على المقالات المنشورة باللغة الانجليزية بدون تحديد لتاريخ النشر، كما تمت مراجعة جميع الحالات للتعرف على الحالات العائلية المتوافقة مع معايير التشخيص الحالية لمتلازمة كلاين– ليفن في الحالات العشوائية.

النتائج: تم العثور على ست مراجعات بحثية و 11 حالة مسجلة وَصَفت بمتلازمة كلاين– ليفن العائلية. وُصفت تفاصيل إكلينيكية في 17 من أصل 29 حالة عائلية تم تحديدها بشكل كاف يؤكد كونها حالات عائلية متوافقة مع وصف متلازمة كلاين– ليفن في التصنيف الدولي الثالث لاضطرابات النوم، بنسخته الثالثة، ومع المراجعات الحديثة لمتلازمة كلاين– ليفن العشوائية.

الخاتمة: تم وصف عدد كبير من حالات متلازمة كلاين– ليفن العائلية تتوافق مع التصنيف الدولي الثالث لاضطرابات النوم، بنسخته الثالثة، ولا تختلف عن الحالات العشوائية. ويقترح أن استخدام التقنيات الجينية الحديثة لدراسة حالات متلازمة كلاين– ليفن العائلية قد يكون ذا فائدة لمعرفة مسببات هذه الحالة النادرة.

Objectives: To highlight the occurrence of familial cases and addresses, whether familial Kleine-Levine syndrome (KLS) presents the same spectrum of disease, as that seen in sporadic KLS.

Methods: Between September and December 2014, reports of familial cases of KLS were identified by searching the Library of Congress, PubMed, and Web of Science databases restricted to the English language, with no restriction on date of publication. All cases were reviewed to identify familial cases consistent with current diagnostic criteria for sporadic KLS.

Results: Six reviews and 11 case reports describing cases of familial KLS were identified. In 17 of the 29 familial cases identified, sufficient clinical details were described to be confident that these cases were familial and consistent with the description of KLS in the International Classification of Sleep Disorders 3rd edition (ICSD-3), and recent detailed reviews of sporadic KLS.

Conclusion: A significant number of familial cases of KLS have been described that are consistent with the ICSD-3 description of KLS, and indistinguishable from sporadic KLS. This suggests that study of familial KLS using modern genetic techniques may be useful in elucidating the pathogenesis of this rare condition.

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Kleine-Levin syndrome (KLS) is rare, but is still the most common form of recurrent hypersomnia with a prevalence of 1-2 per million.[1] The International Classification of Sleep Disorders 3rd edition (ICSD-3)[1] describes KLS as being characterized by "relapsing-remitting episodes of severe hypersomnolence in association with cognitive, psychiatric, and behavioral disturbances". The ICSD-3 diagnostic criteria is shown in **Table 1**. Kleine first described 2 cases of recurrent hypersomnia, hyperphagia, and cognitive disturbance in adolescent boys in 1925,[2] Lewis in 1926,[3] and then Levin in 1929[4] and 1936[5] described further similar cases. Critchley and Hoffman[6] described 2 cases in naval personnel in 1942, and first suggested the eponymous name for the disease: Kleine-Levin syndrome. Critchley later described 9 further cases,[7] describing the onset during adolescence and the trend to spontaneous remission, excluding female cases in this series. Most importantly, as in Kleine's original series, female cases are clearly described, and were no longer excluded from the diagnosis. Further clarity with regard to diagnosis has been provided by a case series described by Arnulf et al,[8] and the reviews of Miglis and Guilleminault[9] and Billiard et al.[10] Despite this progress with definition and diagnosis, the etiology of KLS remains unclear. A number of possibilities have been considered including hypothalamic damage, autoimmunity,[11] and infectious triggers.[12] Familial cases with a preceding history of trauma or brain injury have been described.[13] However, such a history and/or hypothalamic-pituitary endocrine dysfunction is not consistently found.[10] Kleine-Levin syndrome has been associated with human leukocyte antigen (HLA) DR2,[14] and HLA-DQB1*0211,[15] but more extensive studies have failed to confirm HLA disease' associations.[16] Sporadic and familial cases describing an infectious prodrome have been previously described.[17,18] However, no single causative agent has been identified, and it is possible that the initial KLS attack mimics an infectious illness, rather than being associated with infection as recognized by Katz and Ropper.[17] The description of familial KLS suggests a genetic component, either conferring susceptibility, or directly involved in pathogenesis. Investigation of such families may identify genetic loci associated with KLS. This study will review familial cases with careful consideration of diagnostic criteria, to clarify if familial KLS present the same clinical features as sporadic KLS. This is essential to validate extrapolation of findings in familial KLS to the pathophysiology of KLS in general.

Methods. *Literature review.* The Library of Congress, PubMed, and Web of Science databases were searched from September to December 2014, restricted to the English language, using the terms 'Kleine Levin', 'Kleine-Levin', 'Kleine-Levin syndrome', 'periodic hypersomnia', 'Familial Kleine-Levin', 'Familial Kleine-Levin syndrome', 'Twins Kleine-Levin', and 'Twins Kleine-Levin syndrome'. As much of the KLS literature is more than 10 years old, no restriction by date of publication was imposed. This identified 326 articles. Publications referenced in these articles were also reviewed; all publications describing cases with affected family members, or making reference to such cases were selected. Seven reviews (including one book chapter) and 11 case reports documenting familial cases were found.

The diagnosis of familial KLS was reviewed according to the diagnostic criteria described by ICSD-3.[1] Case reports or series with insufficient data to confirm the diagnosis were excluded. In their case control study, Arnulf et al[16] were fastidious in their review of the clinical characteristics. They included 2 of the early reported familial cases,[13,17] and we therefore included these cases here. In keeping with the ICSD-3 classification and approach taken by Arnulf et al[16] and Billiard et al,[10] we have not excluded female cases, and did not consider hyperphagia an absolute pre-requisite for the diagnosis. From the 11 reports describing KLS with affected family members, we have excluded 2 reports. One case cited in the literature as being familial has been excluded as in the original report the affected uncle was described only as having "committed suicide due to asocial behavior".[19] The second report is available in abstract form only, describing 9 family members with KLS over 3 generations.[20] Although the case histories strongly suggest a diagnosis of KLS, the clinical features of each individual case are not described in detail. This series has not therefore been considered further here.

Table 1 - The Third International Classification of Sleep Disorders Diagnostic (ICSD-3) criteria for Kleine-Levin syndrome.

Criteria A - E must be met for diagnosis of Kleine-Levin syndrome	
A.	The patient experiences at least 2 recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks
B	Episodes recur usually more than once a year and at least once every 18 months
C.	The patient has normal alertness, cognitive function, behavior, and mood between episodes
D.	The patient must demonstrate at least one of the following during episodes: 1. Cognitive dysfunction 2. Altered perception 3. Eating disorder (anorexia or hyperphagia) 4. Disinhibited behavior (such as, hypersexuality)
E.	The hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), or use of drugs, or medications

A final report where the affected sib had menstrual related hypersomnia (MRH)[21] has been included and is worthy of comment. It is of note that ICSD-3 reclassifies MRH as menstrual related KLS. The purpose of this review is to highlight the study of familial cases in searching for loci contributing to the pathogenesis of KLS, whilst emphasizing important aspects of such analyses. Studies in autism have emphasized that closely related, but clearly distinct manifestations of a syndrome may have distinct genetic associations. It is therefore important to recognize that, although now clearly described as part of the KLS spectrum, menstrual related KLS may have unique factors contributing to its pathogenesis. Study of such cases using modern genetic techniques may be very informative, and DNA should be collected from such cases. However, in analysis of such cases the possibility of unique genetic contributions should be considered. From the remaining 8 reports describing familial cases we were able to confidently identify 17 cases. Four reports describe sib pairs,[17,18,22,23] including 2 pairs of monozygotic (MZ) twins.[18,23] In a further report, 6 affected members of a Saudi family were described,[15] 5 of whom had classical KLS with one family member with otherwise classical disease episodes, but that were restricted to the puerperium. It is noted that Billiard et al[10] consider episodes of hypersomnia restricted to the puerperium to be more consistent with MRH than KLS. In the 3 remaining reports,[13,24,25] single cases were described and a family history noted. Although the affected family members were not described in detail, sufficient clinical information was recorded to be confident of the diagnosis of KLS in these additional family members. These reports identified 5 additional family members in total. Thus, we have been able to consider 17 reported cases (including one with disease episodes restricted to the puerperium) with 5 additional family members noted also.

Data collection. A recent review[10] commented on the variability in reporting of clinical features of KLS. This is true also of familial cases of KLS with no consistent dataset being reported. The following data have been collected where available: gender; age at onset; family history; medical and psychiatric history (including birth history); HLA typing; number and frequency of episodes; duration of KLS episodes; disease duration, presence and nature of potential precipitating events at KLS onset; events precipitating disease episodes; presence of hypersomnia; eating behavior disorder; sexual behavior disorder; cognitive impairment; hallucinations, delusional states; derealization; mood disorders and irritability; and mood and cognitive impairment between episodes. Finally, the age at remission, and whether this was spontaneous, or drug-related have been recorded.

Results. The publication of the ICSD-3[1] and recent studies[16] and reviews of KLS[9,10,26,27] have set out clear diagnostic criteria. Billiard et al[10] documented 9 cases of familial KLS in their review of 339 cases of recurrent hypersomnia, 239 of which had classical KLS (3.7%). In their series, Arnulf et al[16] commented on 5/104 (4.8%) being familial cases, although does not detail individual cases. This series includes 2 cases reported by Billiard et al.[10] They commented also on the cases of Janicki et al[13] and Katz and Ropper.[17] Dauvilliers et al[11] documented one of 25 cases as having an affected family member. As clinical details specifically of this case are not provided, it has not been considered further here. The case described by Thacore et al[19] has been cited as a case of familial KLS. However, the affected relative (uncle) is described only as having 'attempted suicide after asocial acts', and this is not therefore considered here as a familial case. Rocamora et al[21] described a brother that has KLS, and a sister considered to have MRH. Although clustering of related sleep disorders within a family is of interest, this report has not been considered as a confirmed report of familial KLS, as discussed above. We therefore considered 17 cases of KLS described in the literature as being familial KLS (**Table 2**). These cases conform to the diagnostic criteria for 'sporadic' KLS. However, the diagnostic criteria as set out by ICSD-3 are broad (for example, absence of hyperphagia does not preclude the diagnosis), and the time frame specified in ICSD-2 has been challenged,[10] a similar criterion being retained in ICSD-3. Specific consideration will therefore be given to whether the familial cases identified conform also with the description of sporadic KLS set out in the case controlled study of Arnulf et al,[16] and reviews of Arnulf et al,[27] Billiard et al,[10] and Miglis and Guilleminault.[9] The clinical features for these cases have been summarized in **Table 3**.

In one of the first reports of familial KLS, Suwa and Toru[24] described a 29-year-old Japanese male whose paternal grandmother, father, and older sister had episodes of hypersomnia consistent with KLS. In the grandmother and father, physical and mental fatigue was considered to be triggers, with disease episodes in the sister being preceded by fever. The propositus is described as having episodes of hypersomnia typical for KLS, often preceded by mental and physical exhaustion. A craving for sweet foods preceded disease onset, and many individual disease episodes, and episodes were associated with depression and altered body perception. Intravenous administration of glucose induced 'light sleep' confirmed by EEG. Janicki et al[13] described an

Table 2 - Summary of cases of Kleine-Levin syndrome (KLS) described in the literature as being familial KLS.

Authors	Reported case/s			Additional affected family members, not reported in detail	Comment
	Age, years		Gender		
	Diagnosis	Onset			
Bonkalo 1968[22]	48	16	Female	None	
	32	21	Male		Difficulty waking from adolescence
Suwa and Toru 1969[24]	29	18	Male	Paternal grandmother, father, sister	
Janicki et al 2001[13]	18	18	Female	Male cousin	Paternal aunt with narcolepsy
Katz and Ropper 2002[17]	15	15	Male	None	Brother and sister
	13	13	Female		
Poppe et al 2003[25]	15	15	Male	Maternal uncle	
BaHammam et al 2008[15]	60	17	Male	None	Father and five affected children
	35	15	Female		
	33	16	Male		
	31	16	Male		
	21	21	Female		
	20	15	Male		
Rocamora et al[21]	15	13	Female	None	Related to menstruation
		17	Male		
Peraita-Adrados et al 2012[23]	33	16	Male	None	Monozygotic twins
	33	17	Male		
Ueno et al 2012[18]	15	13	Male	None	Monozygotic twins
	15	14	Male		

18-year-old female patient who experienced a 3-week period of hypersomnia following a minor head injury and consumption of vodka. Mood change and a craving for 'junk food' are described during this episode. A subsequent relapsing remitting course, consistent with a diagnosis of KLS is described with a further episode possibly precipitated by alcohol. The family history included one male cousin who developed KLS at the age of 10 years. One paternal aunt had narcolepsy.

In 2002 Katz and Ropper[17] described a brother and sister with KLS, with a 5-month separation in onset, these being the first familial cases where both affected family members presented for clinical assessment by the authors. The first case is of a 15-year-old boy with a preceding flu like illness without fever. Mechanical eating of salty foods is described during attacks when he is noted to be irritable and withdrawn. During episodes, sensations were described as feeling bizarre, unpleasant, or wrong. Eight episodes are described in 10 months with duration of 7-12 days. Over the next 5 years, disease episodes became less frequent but lasted up to 81 days, with 16 episodes of hypersomnolence over 5 years in total. Episodes were preceded on occasion by stress or slight alcohol intake, but these were not universally implicated. The sister was described as having a disease onset age of 13 years, also with a preceding flu like illness. The mental state described was for her brother, with a persistent sense of unreality and disconnection. Episode duration was initially typical for KLS, but similar to her brother, increased in duration in up to 72 days with 18 spells over 5 years. Both sibs were normal between attacks. No physical abnormalities were described including normal brain imaging. In the brother, during a disease episode, lumbar puncture, positron emission CT, and cerebrospinal fluid hypocretin were normal. Both sibs expressed DR2 and DQ1, and had no response to medication. The authors[17] discuss the possibility of a psychiatric diagnosis with the second sib imitating the symptoms of the first sib, although they believed this to be unlikely. Although the length of the later episodes for both sibs was atypical, this does not preclude a diagnosis of KLS. Most importantly, with regard to the 'infectious' prodrome, these authors[17] comment that these symptoms may be part of KLS, rather than suggesting an infectious trigger.

Bonkalo[22] also describes a brother and sister pair. The sister suffered 8 sleep attacks between the ages of 16 and 21 years lasting 3-11 days. She complained of nausea and occasional vomiting, and her food intake was described as 'poor' to 'good'. Her brother had trouble waking from adolescence with a more protracted episode of daytime hypersomnia at the age of 21 years, and an episode of sleeping for 3 days later the same year. He is reported also as being 'always hungry' although the temporal relationship to the hypersomnia is not known. Although the brother's history is not absolutely

Table 3 - Clinical features reported for cases of familial Kleine-Levin syndrome. In reports where multiple cases are presented. Data for each case are shown separately.

Authors	Age at onset, years	Gender	Hypersomnia			Precipitating event	ED	Mood disturbance	IEC	NIEB	H/D	Treatment	Comments
			Episode duration, days	Frequency of episodes	DD, years								
Bonkalo 1968[22]	16	Female	3 - 11	8/60 months	5	NR	Yes	I, D, C	No	Yes	No	N	Appetite diminished at onset
	21	Male	1 - 3	2/12 months	NR	NR	Yes	I	No	Yes	No	N	Possible adolescent attacks
Suwa and Toru 1969[24]	18	Male	2 - 10	1-2/month	15	S, F	Yes[1]	I, Mute, ABI	No	Yes	No	C, P, I[2,4]	No attacks for 7 months at time of report
Janicki et al 2001[13]	18	Female	14 - 21	2/3 months	<1	HI, A	Yes	I	No	Yes	Yes[2]	N	
Katz and Ropper 2002[17]	15	Male	7 - 81[3]	16/60 months	5	Fl, S, A	Yes[4]	I, AP, W	No	Yes	No	L, S, Me.Mo, C, F, R[1]	
	13	Female	7 - 72[5]	18/60 months	5	Fl	Yes[6]	I, AP, W	No	Yes	No	L, S, Me.Mo, C, F, R[1]	
Poppe et al 2003[25]	15	Male	NR[12]	NR[13]	NR	NR	Yes	I	NR	NR	Yes	L[2]	
BaHammam et al 2008[15]	17	Male	7 - 14	3 each year	33	Fl	Yes	RC	NR	NR	No	N	
	15	Female	7 - 16	2 each year	20	Menstruation	Yes	RC	NR	NR	No	N	Confined to puerperium
	16	Male	10 - 15	3 each year	10	Fl	No	RC	NR	NR	No	N	
	16	Male	8 - 14	3 each year	9	Fl	Yes	RC	NR	NR	No	N	
	21	Female	7 - 14	3 each year	2	Menstruation	No	RC	NR	NR	No	N	
	15	Male	10 - 21	4 each year	4	Fl	Yes	RC, I	NR	NR	Yes	N	
Rocamora et al[21]	13	Female	5 - 7	11/24 months	2	Menstruation	Yes	I, W	NR	NR	No	V, OC	Resolution with OC
	17	Male	7 - 10	8/48 months	4	NR	Yes	I, W, P	No	Yes	Yes	C	
Peraita-Adrados et al 2012[23]	16	Male	Mean 15	1/ 40 days	13	Rhinitis	Yes[7]	I, U	NR	NR	NR	L[1]	
	17	Male	Mean 14	1/40-180 days	14	Breakup of relationship	Yes[8]	I, U, AP	NR	Yes	Yes	L[1]	
Ueno et al 2012[18]	13	Male	7 - 10	1 every month 23 total		Fl[9]	Yes[10]	NR	NR	Yes	NR	L[2]	
	14	Male	5 - 7	1 every 3 months 10 total		Fl[9]	Yes[11]	NR	NR	Yes	NR	L[1]	

NR - not recorded, DD - disease duration, ED - eating disturbance, IEC - intra-episode cognitive, NIEB - normal inter-episode behavior, H/D - hypersexuality/disinhibition, S - stress, F - fatigue, FL - flu-like symptoms, HI - head injury, A - alcohol, I - irritability/argumentative, ABI - altered body image, AP - altered sensation/perception, W - withdrawn, U - unreality, RC - reduced communication, D - depressed, C - confused, P - paranoid, C (in treatment) - carbamazepine, P - phenobarbital, L - lithium, S - sertraline, Me - methylphenidate, Mo - modafanil, C - clonazepam, F - flumazenil, R - risperidone, V - valproate, OC - oral contraceptive. 1 - craving for sweets during some episodes with reduced food intake during remaining episodes, 2) dressed more provocatively, 3) episodes initially 7-12 days lengthening to 81 days, 4) requested salty foods, ate mechanically, finished whatever he was given, 5) episodes initially 7-10 days lengthening to 72 days, 6) compulsive eating, 7) reduced eating, 8) compulsive eating and drinking, 9) received zanamivir for flu, 10) reduced eating and preference for sour foods, 11) uncharacteristic preference for sour foods, 12) although length of initial 3 episodes NR, subsequent episodes of 5 days on lithium and 7 days after stopping lithium recorded. Poor compliance is noted, 13) initial frequency NR but relapse 6 months after stopping lithium with further episode 7 months later. Legend in Treatment column: N - no treatment, 1 - no effect, 2 - reduced frequency, 3 - reduced length, 4 - reduced symptoms, 5 - complete remission

typical of KLS, Billiard et al[26] have reviewed this case, accepting the author's suggestion that this was a 'forme fruste' of KLS. Poppe et al[25] describe a boy presenting shortly after onset at the age of 15 years, whose maternal uncle was reported to have had KLS in adolescence. Typical symptoms are described with megaphagia and an infectious prodrome, disease episodes lasting 8-9 days. There was a possible reduction in frequency with lithium treatment, however, compliance was poor.

Two pairs of MZ twins with KLS have been described. Peraita-Adrados et al[23] described male MZ twins who were 33 years of age at presentation. The first-born twin reported a first episode of hypersomnolence at age 16 years, and a last episode age 29 years. These were typical KLS disease episodes, except for decreased eating. They lasted a mean of 15 days, progressively shortening, with a cycle length of 40 days. The second-born twin experienced a first disease episode at age 17 years after the break up of his first love affair. The last disease episode was at age 31 years. This twin described compulsive eating and sexual disinhibition. Disease episodes for the second twin had a mean duration of 2 weeks with a cycle length of 40 days lengthening to 180 days. Neither twin benefited from lithium. The twins expressed DQB1*0601 as opposed to DQB1*0201, the latter being the DQB

Table 4 - Results of polysomnography, cranial imaging (CI), electroencephalography studies (EEG), and laboratory investigations reported for cases of familial Kleine-Levin syndrome as found in different studies.

Authors			EEG			Laboratory investigations															Comments
	Polysomnography	CI	CSF	Intra episode	Inter episode	ESR	EBV titer	FG	RG	Na	P	Cl	Ca	Mg	Hb	WBC	TSH	EE	MP	
Bonkalo 1968[22]	No data recorded	N		NMA	NMA																
	No data recorded			NMA																	
Suwa and Toru 1969[24]	Reduced REM/ total	N[1,2,3]	N	NMA	NMA			N	N	N	N	N	N	N	N	N					Light sleep induced by iv glucose. Four CSF examinations recorded. Protein and glucose high on some occasions
Janicki et al 2001[13]	No data recorded	N[4]	N	NMA		N		N	N								N		N		
Katz and Ropper 2002[17]	No data recorded	N[4,5]	N	N	N		N											N			CSF hypocretin normal during attack
	No data recorded	N[4]		N	N		N											N			
Poppe et al 2003[25]	Reduced sleep efficiency and reduced REM/total	N[4]								N											NMA
BaHammam et al 2008[15]	No data recorded	N						No data recorded													
Rocamora et al[21]	No data recorded	N[4]		NMA														N	N		
	No data recorded	N[4]		NMA														N	N		
Peraita-Adrados et al 2012[23]	No data recorded	N[4]						No data recorded													
	No data recorded	N[4]						No data recorded													
Ueno et al 2012[18]	Reduced sleep efficiency							No data recorded													
	N							No data recorded													

CSF - cerebrospinal fluid, ESR - erythrocyte sedimentation rate, EBV - Epstein-Barr virus, FG - fasting glucose, RG - random glucose, Na - sodium, P - potassium, Cl - chloride, Ca - calcium, Mg - magnesium, Hb - hemoglobin,WBC - white blood cells, TSH - thyroid stimulating hormone, EE - endocrine evaluation, MP - metabolic panel, REM - rapid eye movement, N - normal, NMA - no major abnormality, 1 - skull x-ray, 2 - pneumoencephalogram, 3 - carotid arteriogram, 4 - magnetic resonance imaging, 5 - single-photon emission computed tomography

allele suggested to be over-represented in KLS.[11] Ueno et al[18] described also male MZ twins with KLS. The first twin presented at age 15 years with the first disease episode at 13 years of age, one month after treatment for influenza with zanamivir. The episodes lasted 7-10 days occurring monthly. This twin described reduced eating with attacks often preceded by flu-like symptoms. Twenty-three episodes had been recorded to the time of the report, with a reduction in frequency with lithium. The second twin described a similar pattern of disease with onset at age 14 years, the first episode again being preceded by influenza treated with zanamivir. These twins expressed DQB1*0302/0601. The largest family, in which the authors[15] studied all affected members, is a multiplex Saudi family with 6 of 12 individuals affected. Diagnoses were carried out according to ICSD-2 criteria, and are consistent with the ICSD-3 criteria. A mean age of onset of 16.7 years, and mean episode duration of 10.7 days were recorded. One female family member experienced disease episodes only during the puerperium. This family was consanguineous with homozygosity for HLA DQB1*02 in 4/6 affected members, and only 2/6 unaffected. However, all but one family member (affected and unaffected) expressed at least one copy of the suggested susceptibility haplotype. Laboratory findings for these cases have not been consistently reported. Data available have been summarized in **Table 4**.

Discussion. Billiard et al[26] stated that published data support a 'strongly genetic basis' for KLS. Elucidation of the nature of this genetic basis may be undertaken by study of sporadic cases. However, a study of familial cases may be a particularly powerful approach. As emphasized by Moghadam and Plazzi[28] when reviewing the genetic basis of autosomal dominant nocturnal

frontal lobe epilepsy (ADNFLE), in order to extrapolate findings in familial cases to sporadic KLS, it is essential to confirm as far as possible, that sporadic and familial cases represent the same condition. The purpose of this article is to review published cases of familial KLS to address whether familial cases have been described that present a typical picture of KLS. Similarly, careful clinical diagnosis and differentiation of subgroups is an essential pre-requisite for genetic studies.

Arnulf et al[8] reviewed 186 published KLS cases, and subsequently carried out a case control study of 108 cases.[16] They found 75.9% of cases to be adolescent boys with an overall mean age of onset of 15.7±6 years (range: 6-59 years) with 81.7% of cases having disease onset in the second decade.[16] Billiard et al[10] documented a male:female ratio of 4.08 in classical KLS, with disease onset before the age of 10 years in 3.7% of cases, and 6.7% after the age of 30 years. In keeping with this, 12 of the 17 cases discussed here were males with 15/17 having onset in the second decade (**Table 2**). The occurrence of 5 female cases presenting with classical features emphasizes the importance of not excluding female patients from this diagnosis. Billiard et al[10] described episode lengths of 1-180 days in men, and 1-60 days in women with significant intra-individual variability. These authors[10] question the validity of the ICSD-2 criterion "recurrence within one year" as they describe cases with otherwise classical KLS with cycle lengths of up to 1095 days in men, and 1460 days in women. Although modified to recurrence within 18 months in ICSD-3, these cases would still lie outside these criteria, despite being typical in all other respects. A decrease in frequency was described in 25.9% of cases with KLS, as seen in some familial cases. The familial cases reviewed in this present study fit comfortably within the spectrum defined in sporadic cases.

Arnulf et al[16] describe 89% of patients as remembering a preceding event, 72% reporting an infectious prodrome, alcohol use in 23%, sleep deprivation in 22%, unusual stress in 20%, or physical exertion in 19%, and head trauma in 9%. Billiard et al[10] describe a significant event at onset in 66.5% of cases with a history suggesting an infectious illness being most frequent. Again the familial cases described here conform to this description.

Billiard et al[10] describe hyperphagia in 66%, or increased food intake in 56% of cases, but decreased appetite in 34%. In keeping with this the ICSD-3 classification[1] describes altered alimentary behavior, rather than hyperphagia. Thus, the description of cases with reduced appetite by Peraita-Adrados et al,[23] Ueno et al,[18] and BaHammam et al[15] does not preclude consideration of these cases in this review of familial KLS. Arnulf et al[16] describe automatic eating in 37% of cases as described for some cases considered here.

The cases reported here accurately reflect the spectrum of cognitive impairment, altered perception, and psychological change reported in the published literature on sporadic KLS. Arnulf et al[16] describe a continuously altered dreamlike perception, as described by one of the familial cases reviewed here, as having a 100% sensitivity for KLS. They describe also the occurrence of a brief 'overshoot' of insomnia, as described in some familial cases. Restoration of normal function between episodes is considered a prerequisite for the diagnosis, and was reported in all cases considered here. Altered sexual drive was considered part of KLS in the early literature. Only 3 of the 17 patients described here were documented as reporting alteration in sexual behavior. However, this is not a prerequisite for the diagnosis based on ICSD-3 criteria,[1] and Arnulf et al[16] found altered sexual behavior in only 59% of cases, when enquiring specifically regarding this criterion. Billiard et al[10] described the 4 classical behavioral 'components' of KLS (hypersomnia, compulsive eating, sexual disinhibition, and odd behavior) to have all occurred during at least one episode in only 14.2% of patients with the first 3 in 30.5% of cases described. A number of authors[15,16] have studied HLA associations in KLS. In their case control study of 104 patients, Arnulf et al[16] found no evidence of preferential transmission of the DRB1*0301-DQB1*0201 and DRB1*0701-DQB1*0202 alleles described as being associated with KLS in a previous smaller study. As discussed above, a multiplex Saudi family has been described, in which 4/6 affected individuals were homozygous for DQB1*02 with only 2/6 unaffected individuals being homozygous.[15] However, homozygosity is not required for HLA alleles to confer susceptibility to autoimmunity, this finding potentially suggesting a linked non-HLA gene to be important.

The main limitations of this study are the variable reporting of clinical features and small number of cases identified. However, inclusion of only studies where sufficient information was presented to be confident of the diagnosis by comparison with international criteria and detailed reviews of sporadic KLS ensures that problems associated with variable recording of clinical features are avoided. Although the number of cases documented are small, the familial cases of KLS described here demonstrate the same pattern of disease as sporadic cases as suggested by Billiard et al.[10] As long as diagnostic criteria set out here are strictly adhered to, study of familial cases, may therefore shed light also on the pathogenesis of sporadic KLS.

There is an 800-4000 fold increased risk of developing KLS in first degree relatives of affected individuals.[27] Shared environmental effects cannot be excluded including common exposure to an infectious trigger. However, even when sibs have both described a preceding infectious illness, the significant difference in time of onset argues against an infectious trigger in these cases. Furthermore, extensive search for infectious triggers in sporadic KLS has not identified a causative agent. The suggestion of a genetic component for KLS is supported by the increased incidence of KLS in the Jewish population,[16,26] possibly due to Jewish specific polymorphisms, or enriched polymorphisms within this population. The description of familial cases reviewed here, including a consanguineous Saudi family with 6 affected individuals, makes enrichment for a polymorphism found widely more likely.

Taken together, these findings argue that genetic analysis of cohorts of individuals diagnosed according to criteria discussed in this review may help to further our understanding of the pathogenesis of KLS. Family studies are appropriate and may facilitate such analyses.

The purpose of this review is to identify cases that could confidently form the basis for genetic analysis of familial KLS. This does not suggest that cases not included here do not represent KLS. More in that it is essential that initial genetic studies focus on cases where diagnostic confidence is highest. Given that many of the cases described in the literature are not available for such studies, it is hoped that this review will set a standard to be considered when further familial cases are identified and considered for genetic analysis.

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