NEW RESEARCH

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Dual Cases of Type 1 Narcolepsy with Schizophrenia and Other Psychotic Disorders

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Objective: Cases of narcolepsy in association with psychotic features have been reported but never fully characterized. These patients present diagnostic and treatment challenges and may shed new light on immune associations in schizophrenia.

Method: Our case series was gathered at two narcolepsy specialty centers over a 9-year period. A questionnaire was created to improve diagnosis of schizophrenia or another psychotic disorder in patients with narcolepsy. Pathophysiological investigations included full HLA Class I and II typing, testing for known systemic and intracellular/synaptic neuronal antibodies, recently described neuronal surface antibodies, and immunocytochemistry on brain sections to detect new antigens.

Results: Ten cases were identified, one with schizoaffective disorder, one with delusional disorder, two with schizophreniform disorder, and 6 with schizophrenia. In all cases, narcolepsy manifested first in childhood or adolescence, followed by psychotic symptoms after a variable interval. These patients had auditory hallucinations, which was the most differentiating clinical feature in comparison to narcolepsy patients without psychosis. Narcolepsy therapy may have played a role in triggering psychotic symptoms but these did not reverse with changes in narcolepsy medications. Response to antipsychotic treatment was variable. Pathophysiological studies did not reveal any known autoantibodies or unusual brain immunostaining pattern. No strong HLA association outside of HLA DQB1*06:02 was found, although increased DRB3*03 and DPA1*02:01 was notable.

Conclusion: Narcolepsy can occur in association with schizophrenia, with significant diagnostic and therapeutic challenges. Dual cases maybe under diagnosed, as onset is unusually early, often in childhood. Narcolepsy and psychosis may share an autoimmune pathology; thus, further investigations in larger samples are warranted.

Keywords: type 1 narcolepsy, psychotic disorders, HLA, brain autoantibodies, autoimmune

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SCIENTIFIC INVESTIGATIONS

Type 1 narcolepsy is a disabling sleep disorder caused by hypocretin-1 deficiency affecting approximately 0.02% of adults worldwide.[1] It is strongly associated with the DQB1*06:02 allele of the human leucocyte antigen (HLA) system,[2] and is likely due to an autoimmune attack causing a specific loss of hypothalamic hypocretin-1 neurons.

Narcolepsy is characterized by the presence of daytime sleepiness, cataplectic attacks, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed nocturnal sleep. Initially narcolepsy was considered a psychiatric disorder, as some symptoms are reminiscent of psychiatric disorders, for instance, disordered thinking and confusion-like behaviors due to sleepiness; and psychotic-like symptoms due to hypnagogic/hypnopompic hallucinations.

Recently, the HLA system has been implicated in schizophrenia through several genome wide analysis studies (GWAS),[3-6] making the study of psychotic symptoms in narcolepsy of special interest, and the possibility of an overlapping autoimmune pathology conceivable. Another finding linking autoimmunity and the emergence of psychotic symptoms has been the description of anti-neuronal surface antibodies in young adults who develop psychosis in the context of limbic encephalitis,[7] especially anti-NMDA-receptor antibodies. These autoantibodies

BRIEF SUMMARY

Current Knowledge/Study Rationale: Rare cases of narcolepsy with psychosis have been reported but never systematically studied regarding clinical features, treatment outcomes, or potential autoimmune markers. We carefully examined a cohort of dual cases to define characteristics of hallucinations and delusions, compared to simple narcolepsy, and searched for antibodies directed against targets known to be involved in other forms of psychosis.

Study Impact: Our study will improve diagnosis and treatment of these complex cases, and provides a specialized questionnaire for clinical use. We found no evidence of antibody-mediated autoimmunity or new HLA associations, but based on our study of clinical history, we make recommendations on how to proceed.

recognize neuronal surface antigens and have a causal relationship with the diseases. Tsutsui et al. detected anti-NMDAR antibodies in three of five hypocretin-deficient narcolepsy patients who had severe psychotic symptoms but no signs of encephalitis.[8] The prevalence of antibodies to other neuronal surface proteins, such as AMPA receptor type 1 or 2, the GABA receptor, and proteins associated with the voltage-gated potassium channel, LGI1 and CASPR2, have not yet been investigated in narcolepsy patients with psychosis.

Comorbid psychiatric symptoms are more frequent in narcoleptic patients than in the general population. Among these, depression is the most frequently reported in adults.[9-11] The frequency of comorbid schizophrenia is unknown, despite the fact that these two disorders have been historically related[12,13] due to the many overlapping symptoms (e.g., hallucinations) and similar ages of onset. Misdiagnosis and inappropriate treatment can be more common than with other psychiatric disorders.[14] In a few cases, narcolepsy has been misdiagnosed as refractory schizophrenia.[15-17] There are also occasional reports of narcolepsy patients with challenging differential diagnoses with a psychotic disorder.[18,19] These highlight the difficulties faced by clinicians to correctly diagnose narcolepsy and psychosis in the presence of vivid hallucinations and altered behavior. Of importance is the presence of cataplexy, the best clinical marker of HLA-associated hypocretin-1 deficiency, a finding not always reported in prior case reports. Cataplexy itself can be difficult to diagnose in the presence of another psychiatric disorder and may be inhibited by antipsychotic treatment.[20,21]

To complicate matters further, there are case reports of narcolepsy with paranoid psychosis emerging after treatment with psychostimulants, suggesting that treatment can also be involved.[22-24] Nevertheless, there are a few reports of individual cases with a proven coexistence of narcolepsy together with a genuine psychotic disorder.[25-27] Other reports do not allow definitive conclusions of whether the association with psychosis is primary, or secondary to stimulant treatments.[25,28-30]

Psychotic symptoms in narcolepsy have been evaluated in three controlled studies. Two studied narcolepsy, schizophrenic patients, and control subjects,[31,32] while another studied narcolepsy patients versus matched controls.[33] Although methodologies were different, the main conclusions were similar: the modality of hallucinations (auditory in schizophrenia vs visual and multisensory in narcolepsy) can differentiate narcolepsy from schizophrenia; and delusions are frequent in schizophrenia, but not present in narcolepsy or control subjects, except for rare instances. Moreover, in striking contrast to psychotic patients, narcolepsy patients experience hallucinations *only* when falling asleep, shortly after awakening, or when they are very sleepy. On the contrary, in psychotic patients hallucinations are more frequent during wakefulness when the patient is more alert.

In this work, we review a rare series of 10 patients with a well-documented diagnosis of narcolepsy together with schizophrenia or another psychotic disorder. Eight patients were diagnosed at the Stanford Center for Narcolepsy (California) over a period of 9 years. In view of the diagnostic challenges we faced in these cases, we developed a questionnaire-based interview tool with the goal of helping clinicians to differentiate true psychosis from psychotic symptoms experienced by narcoleptic patients (Diagnostic Interview for Genetic Studies Adapted for Narcolepsy [DIGSAN]). This questionnaire, modified from the Diagnostic Schedule for Genetic Studies (DIGS)[34] was then tested in narcolepsy cases diagnosed at St. Vincent's hospital in Korea, where two additional cases were identified. Based on the autoimmune basis of narcolepsy, we hypothesized that antineuronal surface autoantibodies could be present in some patients with the dual diagnosis, potentially in a higher proportion than in patients with a diagnosis of psychosis. We therefore performed a systematic study of this unique cohort of dual-diagnosis cases by performing HLA typing and screening for autoimmune markers of the central nervous system (CNS), as well as antibodies linked to systemic autoimmune diseases. The study of narcolepsy cases associated with psychotic disorders may provide novel insights into the pathophysiology of both illnesses that could share an autoimmune mechanism.

SUBJECTS AND METHODS

Stanford and Korean Samples

Eight patients with cataplexy and psychosis were identified from 2003-2012 at the Stanford Sleep Clinic among a total of over 300 diagnosed patients. All presented with typical HLA DQB1*06:02-positive narcolepsy with cataplexy. Diagnosis was confirmed by nocturnal polysomnography (PSG) and a multiple sleep latency test (MSLT). Four of 8 had documented low CSF hypocretin-1. All but one had also been diagnosed with a concurrent psychiatric psychotic disorder by a psychiatrist external to the sleep center. Additional cases were identified within a large cohort at St. Vincent's hospital in Korea (see Testing the DIGSAN below). Of 3 initial subjects, 2 were found to have clear cataplexy and were finally included. For immunological studies, each patient was paired with an ethnically and age-matched control. Sera from all cases and controls were studied blind of diagnosis.

Development of the DIGSAN

Based on the experience with these patients, we built a specialized questionnaire (DIGSAN). It was designed to be as short as possible and clinically usable. Nevertheless, it has to be administered by a clinician or a trained professional in sleep disorders.

The questionnaire is structured in 5 sections: Section I Demographics, section II Family History, section III Narcolepsy symptom survey, section IV Medical History, and section V Psychosis Interview. Material to study psychiatric symptoms was drawn from section K (Psychosis) of the DIGS 3.0 version 03-Nov-1999. Material from section F (Depression) and G (Mania) was added to obtain data regarding incidental mood disorders.

For non-psychiatrist interviewers, it is important to note that for questions in the psychosis interview (section V), particularly numbers 8, 9, and 10, the interviewer has to consider not only the patient's verbal answers, but also other information such as their behavior, as well as input from relatives and clinical records, if available. The DIGSAN was built to help to assign a unique or dual diagnosis for patients with narcolepsy; in the case of a dual diagnosis, a consensus with both a sleep

Table 1—Summary data of patients.

ID	Sex	Race	Age	Age at narcolepsy diagnosis	Sleepiness onset	Cataplexy onset	Age at onset of psychotic symptoms	DSM – TR Psychiatric Diagnosis
M1	F	E	74	25	13	13	20	Delusional Dis
M3	F	E	30	21	8	18	20	Schizoaffective Dis
M5	F	AA	16	16	15	15	16	Schizophreniform Dis
M7	M	E	16	13	12	12	15	Schizophrenia
M13	M	E	18	17	14	15	16	Schizophrenia
M15	F	AA	12	10	10	11	11	Schizophrenia
M19	F	AA/E	34	11	11	11	23	Schizophrenia
M21	M	E	16	15	14	14	15	Schizophreniform Dis
M9 (K)	M	A	40	29	14	14	15	Schizophrenia
M17 (K)	F	A	32	22	15	17	18	Schizophrenia

A, Asian; E, European ancestry; AA, African American.

disorders specialist and a psychiatrist is needed. The questionnaire is included in the supplemental material.

Testing the DIGSAN

We tested the DIGSAN by administering it to 3 patients having a dual diagnosis of narcolepsy and schizophrenia at St Vincent's hospital, Korea, from a cohort of over 300 narcolepsy patients. Methods for the cohort evaluation were reported in Hong et al.,[35] although the sample has been continually extended through 2012. Of these 3 subjects, 2 were found to have clear cataplexy based on the DIGSAN and further review, and were included.

Screening of Autoantibodies Associated with Systemic Autoimmune Diseases

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence (IFI) on Hep2 lines (INOVA, San Diego, USA). ANA titers < 1:160 were considered negative. Anti-ENA and anti-Ribosomal P antibodies were screened by line immunoblot assay (Innogenetics, Gent, Belgium), and reactive sera were studied by a semiquantitative ELISA for specific antigens: SSA, SSB, U1RNP, or Sm (INOVA) or a quantitative ELISA (for Scl70 or Jo1)(Phadia AB, Uppsala, Sweden).

In ANA positive samples with a homogeneous pattern, we tested for the presence of anti-double-stranded DNA (dsDNA) antibodies by IFI on *Crithidia luciliae* slides (INOVA).

Onconeural Antibody Detection

Onconeural antibodies were screened by IFI, at 1:10 titer, on rat cerebellum sections (Euroimmun AG, Luebeck, Germany). Primate cerebellum slides (Euroimmun AG) were used to confirm positive reactions on rat cerebellum.

We also tested antibodies to 9 known intracellular synaptic antigens: amphiphysin, GAD65, Hu, Yo, CV2, Ri, Ma1, Ma2, and SOX-1, by line immunoblot assay (RAVO Diagnostika, Freiburg, Germany).

Neuronal Surface Antibody Detection

Neuronal surface antibodies (NSAbs) were studied by a "Cell Based Assay" (CBA), according to the method of Wandinger et al.[36] Serum samples were tested at a starting dilution of 1:10, by IFI, on rat cerebellum and hippocampus sections and transfected HEK293 cells. HEK293 cells expressed one of these antigens: the glutamate receptor type NMDA (subunit NR1), the AMPA receptor type 1 or 2, the GABA receptor, or one of the proteins associated to the voltage-gated potassium channel: leucine-rich glioma inactivated 1 (LGI1) or Contactin associated protein 2 (CASPR2) (Euroimmun AG).

All tests were performed blindly and IFI images interpreted independently by two observers

HLA Typing

A, B, C, DR, DQ, and DP typing was conducted in all cases with (i) cataplexy or hypocretin-1 deficiency and (ii) long standing psychosis, totaling 10 samples. High-resolution typing was obtained using the Luminex xMAP Technology. Allele frequencies were obtained from http://bioinformatics.nmdp.org/ and other sources.

RESULTS

Clinical Data

Demographic, sleep clinical, and psychiatric diagnostic data for the patients are summarized in **Tables 1**, **2**, and **3**, respectively.

Regarding narcolepsy, all cases were typical type I narcolepsy patients. Age of onset was younger than usual, including 4 children (younger than 12 years) and 6 adolescents (12-18 years). Clinically, patients had the complete clinical "tetrad" of symptoms, except for one patient who did not report sleep paralysis. Somnolence was severe as shown by a high Epworth Sleepiness Scale score (typically > 20) and short mean sleep latencies during MSLTs (< 2 minutes). All had hypnagogic/hypnopompic hallucinations that were multisensory (visual, kinesthetic, olfactory, gustative) and related to drowsiness or sleep onset.

Regarding psychosis, patients were formally diagnosed according to DSM-IV-TR criteria as: schizophrenia (6 patients), schizoaffective disorder (1 patient), schizophreniform disorder (2 patients) and delusional disorder (1 patient). In all cases but

Table 2—Narcolepsy data.

ID	HH	SP	Epworth	PSG SOREM	Sleep latency	HLA DQB1*06:02	CSF Hcrt-1 levels
M1	yes	yes	18	n.a.**	n.a.	+	n.a.
M3	yes	yes	21	3/4	1 m 40 sec	+	0
M5	yes	yes	21	3/4	1 m 30 sec	+	n.a.
M7	yes	no	22	2/3	1 m 50 sec	+	n.a.
M13	yes	yes	13*	2/4	1 m 55 sec	+	0
M15	yes	yes	22	n.a.**	n.a.	+	n.a
M19	yes	yes	22	yes night PSG	1 m 50 sec	+	0
M21	yes	yes	22	5/5	1 m 20 sec	+	0
M9	yes	yes	15	3/5	24 sec	+	0
M17	yes	yes	18	5/5	1 m 25 sec	+	0

HH, hypnagogic hallucinations; SP, sleep paralysis; Epworth, Epworth sleepiness scale; PSG SOREM, sleep onset REM periods on polysomnography; n.a., not available. * With stimulants selegiline. ** Not available, although polysomnography and MSLT were performed in another sleep center and reported positive by history.

one, diagnosis was made by external psychiatrists who provided psychiatric follow-up. Case M7 was diagnosed at the Stanford Sleep Clinic by EM, but he and his family rejected psychiatric diagnosis and were lost to follow-up.

All cases except M1 had persistent auditory hallucinations during the wake period and presented with typical features of schizophrenia paranoid type: disorganized thinking and behavior and delusions. Auditory hallucinations were of paranoid and mystic content, and all of the patients also had delusional ideas, the majority being persecutory, with increased suspicions and ideas of reference. All patients reported florid and severe hypnagogic hallucinations and vivid dreaming, consistent with those observed in narcolepsy; however, these occurred not only at sleep onset, but also frequently during daytime. In addition, they were chronically convinced of the reality of the hallucinations. There was typically an absence of insight regarding these ideas. In several cases, family and psychiatric records described anxiety and sadness. Flat affect was described in 5 of the patients. Patients also had disorganized behavior, tended to avoid social contacts, and had difficulties in their social lives and relationships. All had academic and/or work difficulties and demonstrated less personal and social achievement than could be expected by their age and cultural level even compared to other narcoleptic patients.

Table 3 describes the clinical history and particular clinical features of each of these patients, with psychiatric treatment and the outcome of psychotic symptoms when available.

Four cases carried additional comorbid psychiatric diagnoses: learning disabilities (2), eating disorder (anorexia nervosa) (1), and drug abuse (1). The last patient was the only one who presented with unusually aggressive behavior. Four of the 10 cases had family history of narcolepsy (2) and psychiatric disorder (3). One patient (M15) had antecedents of both narcolepsy (aunt) and psychiatric disorder (brother, autism); she also had G6PD deficiency and learning disability due to abnormal auditory processing. She also had the earliest onset of psychotic symptoms; was diagnosed with early onset schizophrenia, and the psychiatrist initiated aripiprazole with a good control of psychotic symptoms.

Onset of psychotic symptoms generally followed narcolepsy, although it was concomitant in several cases, particularly in early onset cases, and within 3 years in all other cases except M1 and M19. Two patients had psychotic symptoms for less than 6 months at the time of the study (M5, M21), and thus have a provisional diagnosis of schizophreniform disorder. Obesity, a common feature of childhood narcolepsy, was present in 4 cases, and 2 were treated with continuous positive airway pressure (CPAP).

All patients, except Korean case M9, started treatment for narcolepsy before the antipsychotic treatment. Treatments used were: sodium oxybate, and stimulants alone (modafinil, methylphenidate, selegiline) or combined with antidepressants as fluoxetine and venlafaxine. In none of these cases did delusions and auditory hallucinations improve after cessation of narcolepsy treatment. In one case (M1), there was a clear relationship between treatment initiation and increase of psychotic symptoms. This patient had persecutory and jealous delusions for several years; the delusions became more visible after initiation of treatment with sodium oxybate. Another case, M19, had a long history of narcolepsy-cataplexy, was intolerant of stimulant medication, and developed psychosis many years after onset. The response to antipsychotic therapy was highly variable in these patients, ranging from excellent (M3, M15) to very poor (most others), with frequent refusal of psychiatric therapy.

Autoantibody Testing

Only serum n.4 was ANA positive, and presented a dense speckled fine pattern, compatible with the presence of anti-DSF70 antibodies, which is a frequent ANA pattern found in healthy people and not associated with systemic autoimmune diseases.

Autoantibodies directed to specific antigens linked to systemic autoimmune diseases (ENA, Ribosomal P or dsDNA) were negative in all sera.

Immunostaining of rat cerebellum showed a positive reaction only in serum n.13, which yielded a granular cytoplasmic pattern in Purkinje cells. We ruled out the presence of anti-Yo antibodies using line immunoblot studies. This serum sample did not present a positive immunofluorescence pattern on primate cerebellum, and we interpret these results as an artifact reaction due to a heterophilic antibody against a rat antigen. None

Table 3—Psychiatric description of patients.

	Other Diagnoses	Family History	AH	Del.	Marital status	Years education	Present occupation	Living	Particular features of clinical history, psychiatric treatment, and outcome of psychotic symptoms
M1	Hypothyroidism, depression	n.a.	yes	yes	widow	8	retired	Alone	Long history of delusional disorder, jealous type. Some auditory hallucinations of jealousy content and delusions increased in intensity when initiating sodium oxybate. Psychiatrist prescribed aripiprazole but discontinued due to side effects (somnolence). No treatment currently, delusions persist but at lower level.
M3	Migraine, obesity, sleep apnea, depression, anxiety	No	yes	yes	single	14, Bachelor degree in Fine Arts	retired	With parents	Auditory hallucinations commenting on her bad behavior, messages received from the Bible, disorganized thoughts began after modafinil treatment. Comorbid depression. Hospitalized in psychiatry several times, treated with risperidone, venlafaxine and valproic acid, uses CPAP. Recently admitted to a group home for psychiatric care.
M5	Obesity	No	yes	yes	single	10	student	With parents	First hospitalized for "drop attacks"; diagnosed with narcolepsy-cataplexy with severe insomnia, hypersomnolence, and sleep related multisensory hallucinations. Sodium oxybate improved insomnia and somnolence. Fluoxetine was prescribed for remaining cataplexy with emergence of severe auditory hallucinations and disorganized thoughts. Now treated with risperidone, sodium oxybate, and venlafaxine. Auditory hallucinations persist.
M7	Obesity, Sleep Apnea	No	yes	yes	single	14	student	With parents	First diagnosed as depression then confirmed as narcolepsy-cataplexy; sleep apnea treated with CPAP. Has imaginary friends talking to him, introverted, socially withdrawn, poor eye contact. Partial critique of delusions and hallucinations. Family refused psychiatric treatment. Lost to follow-up.
M13	Cannabis / alcohol abuse	No	yes	yes	single	9	no studies not working and also not seeking work	With parents	One year after narcolepsy diagnosis, was treated with selegiline, and then became suspicious with persecutory ideas of sexual abuse, aggressive against family, with auditory hallucinations. Abuse of cannabis and alcohol. Multiple psychiatric hospitalizations. Treated first with various antidepressants with improved cataplexy but no resolution of delusions. Olanzapine improved delusions but increased somnolence. Stopped antipsychotics with exacerbation of psychotic symptoms. Lost to follow up.
M15	Auditory learning disability, G6PD deficiency	Brother with autism; Aunt with narcolepsy	yes	yes	single	8 adapted school	student	With parents	Anxious since childhood, learning disability; hospitalized for possible epilepsy, EEG was negative. A diagnosis of narcolepsy was made a year later; significant hypnagogic hallucinations with partial self-awareness. Initiated treatment with Modafinil, which produced racing thoughts and increased hallucinations, poor eye contact. Aripiprazole was used with a significant improvement.
M19	Eating disorder, multidrug allergies	No	yes	yes	single	16	unemployed	Alone	Long history of narcolepsy cataplexy; artistic irregular work; independent means with travel between Europe and America. Progressive deterioration with persecutory ideas, auditory hallucinations, megalomania. Refused all treatment with antipsychotic drugs, disorganized behavior, now frequently hospitalized in Psychiatry in a European country.
M21	Learning disability, traumatic brain injury, obesity	Grand Mother committed suicide / Father alcohol abuse	yes	yes	Single	8 adapted school	student	With parents	Frontal contusion following head trauma at age 13 with memory loss and headaches for six months; 1 year later developed severe sleepiness and multisensory hallucinations, including auditory hallucinations; blunted affect. Treated with modafinil, methylphenidate, and sodium oxybate; narcolepsy symptoms improved but he became increasingly aggressive. Symptoms improved after stopping stimulants but not the auditory hallucinations. Antipsychotic treatment under consideration.
M9 (K)	Atopic dermatitis	n.a.	yes	yes	Single	10	not working and also not seeking work	With parents	From age of 14, he suffered from excessive daytime sleepiness. At 15 started treatment for atopic dermatitis and blamed his excessive sleepiness on allergic symptoms. Gradually withdrew from social contacts. First psychiatric admission at the age of 15, diagnosed as a prodromal stage of psychosis, then developed auditory hallucinations, aggressive behavior, self-talking, silly smile, functional impairment. Treated with antipsychotics and antidepressants. Diagnosis of narcolepsy was made at the age of 29 improved with modafinil. Now no treatment.
M17 (K)	No	Father depression, cousins psychotic disorder	yes	yes	Single	14	unemployed	With parents	Suffered from hypnagogic hallucinations and sleep attacks from age 15, intermittent treatment for narcolepsy. First psychiatric ward admission at 18, for auditory hallucinations and persecutory delusions. She has been continuously treated with antipsychotics, and hospitalized several times because psychotic relapses, and has never been symptom free. Now stable with aripiprazole and methylphenidate

AH, auditory hallucinations; Del., delusions.

of the samples showed the characteristic anti-aquaporin 4 pattern on cerebellum slides. Immunofluorescence on hippocampus sections and specific CBA tests were negative in all sera.

HLA Typing

No shared HLA allele was found (see **Table S1**, supplemental material). The frequency of HLA C*01:02, an allele previously reported to be associated with schizophrenia in a large cohort of patients, was not increased versus what could be expected, as none of the patients carried this particular allele. Similarly, the carrier frequency of the protective haplotype DRB1*03:01, DQA1*05:01, DQB1*02:01 (30%) was unremarkable and slightly increased versus what would be expected in controls (approximate allele frequency in such a mixed group: 10%). Two unusual findings were the observation of an absence of DRB4 genes (and associated DRB1*04, DRB1*07, and DRB1*09), and a high number of DRB3*03 alleles (80%), a finding that would need a much larger sample to confirm.

DISCUSSION

The co-occurrence of narcolepsy with psychotic symptoms raises clinical and pathophysiological questions. At the clinical level, narcolepsy can be misdiagnosed as a psychiatric condition, especially if cataplexy is not reported, or is unrecognized by the physician. In adolescents, misdiagnosis often results from overlapping age of onset and symptoms (notably hallucinations, and behavioral problems) between narcolepsy and schizophrenia.[14,16,27] The fact that adolescents often go through difficult maturational issues often further confuses the picture, especially when communication is poor and when patients refuse treatment or the reality of the condition. In our case series, narcolepsy symptoms began during childhood or adolescent years but was often not diagnosed for years, and in a number of cases, was not identified until after psychotic symptoms had manifested (**Table 1**). Recently the diagnostic delay for narcolepsy has dramatically shortened, with diagnosis occurring close to onset (childhood and adolescence), emphasizing the importance of differentiating emerging and evolving symptoms of narcolepsy vs schizophrenia.

Prepubertal children pose special diagnostic problems. When cataplexy or atonia episodes are preeminent, a misdiagnosis of Pediatric Autoimmune Neurological Disease associated with Streptococcus (PANDAS), seizures, or paraneoplastic syndrome can be made.[37] Indeed, the characteristics of emergent cataplexy in children are quite different from those of established cataplexy, complicating diagnosis.[38] Irritability, anger, and at times violent behaviors, all secondary to sleepiness, may emerge suddenly in a child who was previously well-behaved and has gained large amount of weight. The change in character can be dramatic but is entirely reversible when treating sleepiness and REM-related symptoms. When hypnagogic hallucinations are preeminent, young children, depending on their maturational stage, may not be able to fully comprehend that these are unreal experiences, especially just after waking up. In most cases, however, children accept that these are similar to dreams once explained carefully by the clinician—a critical difference compared to schizophrenia or true psychotic disorder. Based on the above, when in doubt and unless proven otherwise, it is always better to treat narcolepsy first, hoping all psychotic

Table 4—Clinical characteristics of previously published dual cases.

Reference	Age, sex	Diagnosis, age of symptom onset		Clinic, Treatment, and Outcome of Psychotic symptoms
		Psychotic disorder	Narcolepsy/cataplexy	
Pfefferbaum 1977	54, M	Paranoid schizophrenia, Unk	Clinical, Unk	Paranoid psychosis of unclear onset in relation to amphetamine treatment, which worsened psychotic symptoms; was treated with various antipsychotic drugs, and later developed tardive dyskinesia
Ullman 1977	50, M	Schizoaffective disorder, Unk	Clinical, 40	Tricyclic antidepressants (TCA) and amphetamine ameliorated narcolepsy, but auditory hallucinations persisted
Schrader 1984	67 M	Paranoid Psychosis, Unk	Clinical, Unk	Paranoid psychosis started 4 years after amphetamine treatment, received antipsychotic drugs, developed tardive dyskinesia and major depression
Cadieux 1985	32, M	Paranoid schizophrenia, Unk	Clinical, 12	Symptoms started following stimulant therapy, persistence of psychotic symptoms in the absence of stimulant medication. Later developed tardive dyskinesia
Silvestri 1991	14, F	Psychosis not specified, 11	Clinic, MSLT, HLA, 11	Psychotic symptoms started after treatment with TCA for cataplexy, and subsequently improved with antipsychotic treatment. Recurrent delusional episodes and depressive mood persisted for 9 months after treatment withdrawal and behavioral therapy alone.
Kishi 2004	25, F	Schizophrenia, 19	Clinical, MSLT, HLA, 13	Presented with narcolepsy and psychotic symptoms. Was treated with antipsychotic but those worsened sleepiness, leading to stopping medication. Stimulants were subsequently introduced and improved narcolepsy symptoms, without changing psychotic symptoms. Was later lost to follow-up.
Walterfang 2005	25, F 23, M	Schizophreniform psychosis, 24 Schizophrenia, 21	Clinic, MSLT, 17 Clinic, HLA, 13	Presented with delusional ideas of persecution; considered narcolepsy-related before initiation of stimulants. Delusions remitted only with addition of antipsychotic medication. Psychotic symptoms started two years after stimulant treatment. Thought disorder and disorganization present. Symptoms remitted with antipsychotic drugs.
Kondizella 2006	38, F	Schizoaffective dis, 18	Clinical, MSLT, HLA, low CSF hypocretin, 17	Untreated narcolepsy until age 38, psychotic symptoms treated with typical and atypical antipsychotic and TCA. Addition of stimulants improved narcolepsy symptoms.
Undurraga 2009	27, M	Schizophreniform disorder, 27	Clinical, MSLT, HLA, 21	Stimulants were initiated first, then antipsychotics. These resolved psychotic symptoms but increased somnolence; lost to follow-up
Tsutsui 2012	58, M 37, F 24, F	Delusional Dis and Parkinson Dis (PD) Schizophrenia Schizophrenia	Clinical, MSLT, HLA, Low CSF hypocretin-1 Antibody panel positive for anti NMDA receptor antibodies in all cases	The first patient was diagnosed as PD at the age of 45; narcolepsy diagnosed and treated with methylphenidate at 55. Psychotic symptoms started at 57 and persisted. The two other narcolepsy patients have psychotic symptoms fulfilling criteria of both narcolepsy-cataplexy and schizophrenia. No seizures or clinical/imaging findings suggesting limbic encephalitis

symptoms are narcolepsy-related rather than the converse, especially if the premorbid personality was entirely normal.

The focus of this report are the rare cases in which narcolepsy is genuinely associated with schizophrenia or other psychotic disorders unrelated to the dream-like multisensory hallucinations characteristic of the narcolepsy syndrome. In these cases, we found that the auditory hallucinations appear always together with multisensory (visual, kinesthetic, olfactory, gustative) ones, and complex delusions (persecutory ideas, increased suspicions, ideas of reference) are present. Thinking may be disorganized, although this can be difficult to demonstrate when the individual is very sleepy. In these dual diagnosis cases, the patient generally believes the hallucinations and delusions are real and cannot be easily convinced otherwise. Two possible options then need to be considered: the psychosis may be a side effect of treatment, or the development of an unrelated psychiatric comorbid condition.

Table 4 reviews the few previously published cases of narcolepsy associated with psychosis. As in our case series, narcolepsy onset typically preceded the onset of psychotic symptoms. In many of these older reports, it is difficult to evaluate whether therapy played a crucial role in the development of psychosis.

Until recently, stimulant therapy was the main treatment for narcolepsy, and these compounds are well known to trigger psychosis.[39] Psychotic symptoms may be induced most often by amphetamine or methylphenidate, but also modafinil.[40-44] In this case series, we believe medication was likely a minor factor in the development of psychosis, except in patient M1. In this instance, the diagnosis was delusional disorder rather than schizophrenia, thinking remained organized, and ideation was of the jealous type. In other cases, treatment with antidepressants, stimulants or sodium oxybate may have contributed to precipitating the condition or exacerbated a preexisting one; although it is also possible the underlying schizophrenia became more evident as sleepiness lifted with treatment. Similarly, these patients also had florid hypnagogic hallucinations, which may have fueled the schizophrenia-type delusions without being the sole cause. In several cases close to onset, it is also difficult to exclude the possibility of a natural evolution of the disorder with time, independent of treatment.

In four cases, additional comorbid psychiatric diagnoses were present: learning disabilities, eating disorder, and drug abuse. Four cases had family history of narcolepsy or psychiatric disorder, and one had antecedents of both narcolepsy and psychiatric disorder. This suggests a double diagnosis should be considered, particularly in subjects with known risk factors associated with development of psychosis: family psychiatric history, low intelligence level, personal history of head injury,[45] environmental distress, and cannabis use.[46] The findings in our series agree with previous findings reported in **Table 4**. Silvestri described a girl with a narcolepsy onset at age 11 who had psychiatric family antecedents of psychosis.[26]

All of our dual diagnosis cases except M1 had persistent auditory hallucinations during the wake period, an uncommon

feature in narcolepsy. Moreover, they were chronically convinced of the reality of the hallucinations. Importantly there was an absence of insight regarding these ideas as is typical of patients with chronic psychosis. In addition, our patients tended to avoid social contacts and experienced difficulties in their professional and social lives and relationships.

Treatment response for the dual diagnosis patients was variable and involved balancing narcolepsy therapies to reduce cataplexy, REM-like hallucinations, and sleepiness with antipsychotic drug treatment, which reduces delusions and hallucinations but induces sleepiness. It is important to evaluate the existence of delusional ideas that may be hidden by the patient. Treatment with stimulants alone can worsen psychotic symptoms,[40] but in our experience, stimulant can be used if no overstimulation results. Regarding non-narcolepsy psychotic symptoms, aripiprazole was used, as it is less sedating. In other cases, risperidone was successfully used. It is our experience that undertreating narcolepsy is more often the end result, as untreated sleepiness reduces behavioral problems.

The frequency of hypocretin deficiency in association with schizophrenia is unknown. While co-occurrence is reportedly low, dual cases may be more frequent as a result of misdiagnosis. Clinicians should be mindful that the two syndromes can coexist, and that at minimum one diagnosis does not exclude the other. We believe the DIGSAN can be a useful tool for clinicians to distinguish each separate diagnosis. This is particularly important now that biological tests are available,[47] and others will be developed soon. Accurate diagnosis is critically important for the outcome, as treatment is different for the two diseases, and good treatments are currently available for each illness.

The coexistence of narcolepsy with schizophrenia also raises interesting pathophysiological questions. It may be a chance finding, or an association of two co-clustering autoimmune diseases, as often found in other cases where specific autoimmune diseases can coexist more frequently than expected by chance alone. A large number of HLA association studies in small schizophrenia samples have produced controversial results.[6] One suggested that DR15 or DQB1*06:02 were more frequent in schizophrenia versus controls,[48] although this was not consistently replicated.[49] More recently, using large samples of schizophrenia cases and controls, GWAS studies found clear signals in the HLA region.[3-6] Due to the high level of linkage disequilibrium in the region, the signal has been difficult to map, but it is interesting to note that HLA DRB1*03:01 and DRB1*13:03 appeared to confer protection for the illness,[3,5] while DQB1*06:02 frequency was slightly increased. More recently, carriers of the rare HLA C*01:02 allele have been reported to be at increased risk,[3] a finding that awaits replication. In this study, we fully HLA typed 10 cases with narcolepsy and psychotic disorder, but no clear association emerged in addition to the expected DQB1*06:02 narcolepsy association; notably we did not find increased HLA C*01:02 nor a protective effect of DRB1*03:01, which was, if anything, increased in frequency. These results indicate that psychosis in these dual diagnosis patients is either a chance finding not related to autoimmunity, or mediated through DQB1*06:02. Alternatively, further heterogeneity in schizophrenia associated with these cases may have masked the association in this small sample.

In our series we failed to identify anti-NMDA-receptor antibodies described by Tsutsui et al.[8] in three of five hypocretin-deficient narcolepsy patients with severe psychotic symptoms. We also examined other potential CNS targets and antibodies linked to systemic autoimmune diseases, including the AMPA receptor type 1 or 2, the GABA receptor, proteins associated with the voltage-gated potassium channel, LGI1 and CASPR2, but we could not find any abnormalities. Immunocytochemical studies of brain sections were also conducted without positive results.

In addition to surface and cytoplasmic/synaptic neuronal antibodies, we also screened for antibodies linked to systemic autoimmune diseases (ENA, ribosomal P, dsDNA). Some of these have not previously been studied in narcolepsy and are associated with central nervous system involvement. The rationale is that these studies provide an indirect assessment of patients' autoimmune background, and help to discriminate whether immunofluorescence patterns found on hippocampus or cerebellum sections are due to non-organ-specific vs neuronal-specific antibodies. Again, no abnormalities were identified in our case series.

In conclusion, narcolepsy associated with genuine psychosis is a clear entity that presents specific diagnostic and therapeutic challenges. In our present study, we were unable to substantiate the hypothesis that the psychosis is autoimmune-mediated. Importantly, however, we only examined sera for the presence of autoantibodies and did not explore a potential pathology mediated by cytotoxic T cells. In narcolepsy, autoantibodies have not been consistently found in sera or CSF[50,51]; however, there is now clear evidence of T cell mediated destruction of hypocretin cells.[52] It is therefore possible that a similar cell-mediated mechanism may precipitate schizophrenia in these cases, warranting additional pathophysiological and therapeutic investigation.

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SUPPLEMENTAL MATERIAL

Table S1—HLA typing results in 10 patienst with narcolepsy and long standing psychosis

ID	A-1	A-2	B-1	B-1	C-1	C-2	DRB1-1	DRB1-2	DRB345-1	DRB345-2	DQA1-1	DQA1-2	DQB1-1	DQB1-2	DPA1-1	DPA1-2	DPB1-1	DPB1-2
Mignot-1	02:01	03:01	07:02	40:02	02:02	07:02	11:01	15:01	3*02:02	5*01:01	05:05	01:02	03:01	06:02	01:03	01:03	04:01	04:01
Mignot-3	01:01	02:01	08:01	40:01	03:04	07:01	03:01	15:01	3*01:01	5*01:01	05:01	01:02	02:01	06:02	01:03	01:03	04:01	04:01
Mignot-5	01:01	03:01	07:02	35:01	04:01	15:05	03:01	15:03	3*01:01	5*01:01	05:01	01:02	02:01	06:02	02:01	02:01	13:01	01:01
Mignot-7	01:01	03:01	07:02	44:02	05:01	07:02	04:01	15:01	4*01:01	5*01:01	01:02	03:01	03:01	06:02	01:03	01:03	02:01	04:01
Mignot-9	02:06	24:02	40:01	48:01	03:04	03:04	14:01	15:01	3*02:02	5*01:01	01:02	01:01	05:03	06:02	02:02	01:03	05:01	02:01
Mignot-13	03:01	26:01	07:02	40:02	02:02	07:02	15:01	15:01	5*01:01	5*01:01	01:02	01:02	06:02	06:02	01:03	01:03	04:01	04:01
Mignot-15	23:01	33:03	15:16	81:01	14:02	18:01	11:01	15:03	3*02:02	5*01:01	01:02	01:02	06:02	06:02	01:03	02:01	03:01	17:01
Mignot-17	02:01	26:03	15:01	15:11	03:03	03:03	14:05	15:01	3*02:02	5*01:01	03:01	01:02	03:03	06:02	02:02	02:01	13:01	05:01
Mignot-19	01:01	03:01	44:02	53:01	04:01	05:01	03:02	15:01	3*03:01	5*01:01	04:01	01:02	04:02	06:02	02:02	01:03	04:01	01:01
Mignot-21	03:01	03:01	08:01	39:01	07:01	12:03	03:01	15:01	3*01:01	5*01:01	05:01	01:02	02:01	06:02	02:01	01:03	06:01	01:01

Digs 3.0/Mod
2012

DIAGNOSTIC INTERVIEW FOR GENETIC STUDIES ADAPTED FOR NARCOLEPSY (DIGSAN)

NOTE: THE INTERVIEW CAN BE DONE DIRECTLY WITH THE PATIENT OR WITH THE HELP OF A FAMILIY MEMBER (NOTABLY IN CHILDREN) USE JUDGEMENT IF THE PATIENT IS NOT COMMUNICATIVE

PLEASE NOTE THAT THE TEXTS IN ITALICS MAY REFER TO LITERAL EXPLANATIONS FOR THE PATIENT

SECTION I. DEMOGRAPHICS

SITE ID: ☐☐ **FAMILY ID:** ☐☐☐☐

SUBJECT ID: ☐☐☐☐☐

SUBJECT NAME: _____ _____ _____
First Middle Last

INTERVIEW DATE: ☐☐☐ ☐☐ ☐☐☐☐
M O N D D Y E A R

DATE OF BIRTH: ☐☐☐ ☐☐ ☐☐☐☐
M O N D D Y E A R

INTERVIEWER: **Male** **Female**
Circle sex

		Code Response
RACE:	**1. American Indian / Alaskan Native**	1 2 3 4 5 6
	2. Asian / Pacific Islander	
	3. Black (Non Hispanic)	
	4. Hispanic	
	5. White (Non Hispanic)	
	6. Other / Unknown	

INITIAL or RETEST: I R

IN PERSON or TELEPHONE: P T

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

SECTION II. FAMILY HISTORY

1) *Do you have any family members diagnosed with*

Yes No

a. Narcolepsy-cataplexy?

If yes, describe who is affected and the corresponding symptoms:

_____

_____

b. Depression, psychosis (ex. Bipolar disorder, schizophrenia), or any serious psychiatric disorder? Yes No

If yes, describe who is affected and the corresponding disorders and symptoms:

_____

_____

2) *Were you adopted?* No Yes Unk

3) *In which country were you born?*

4) *What is the ethnic background of your biological parents?*

Code up to four ethnicities on maternal and paternal sides if possible

Mother: _____ _____ _____ _____

Father: _____ _____ _____ _____

5) *What is your current marital status?*

a. Married
b. Separated
c. Divorced
d. Widowed
e. Never married

6) *How many living children do you have?* _____

7) *How many years of school did you complete?* Years

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

Record response: _____

8) *Are you living alone or with others?* No Yes Unk

a. Alone
b. With partner (for at least one year), but not legally married
c. In own home with spouse and/or children
d. In home of parents or children
e. In shared home with other relatives or friends
f. In Residential Treatment Facility
g. Other, Specify: _____

9) *Have you ever been in the Military?*

If no: *Were you ever rejected for Military Service?*

Why? _____

10) *What is your present occupation?*

Record response: _____

10.a) *What is the most responsible job you have ever held?*

Record response: _____

10.b) *If subject is not Head of Household: What is/was the occupation of the head of household most of their working career?*

Record response: _____

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

SECTION III. NARCOLEPSY SYMPTOM SURVEY

1. *How often do you (or your child) have difficulty staying awake during the day?*
☐ Once, or more, per day ☐ Several times per week ☐ Once per week
☐ Once per month ☐ Once per year, or less ☐ Never

2. *How often do you (or your child) experience sudden sleep attacks that are so intense that you must stop what you are doing to or take a nap?*
☐ Once, or more, per day ☐ Several times per week ☐ Once per week
☐ Once per month ☐ Once per year, or less ☐ Never

3. *How often do you (or your child) nap?*
☐ Once, or more, per day ☐ Several times per week ☐ Once per week
☐ Several times per month ☐ Once or less per month ☐ Never

Epworth Sleepiness Scale

How likely are you (is your child) to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you (your child) have not done some of these things recently, try to work out how they would have affected you (him/her). Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze; **1** = Slight chance of dozing
2 = Moderate chance of dozing; **3** = High chance of dozing

SITUATION	CHANCE OF DOZING			
a. Sitting and reading	0	1	2	3
b. Watching TV	0	1	2	3
c. Sitting inactive in a public place (e.g., a theater or meeting)	0	1	2	3
d. As a passenger in a car for an hour without a break	0	1	2	3
e. Lying down to rest in the afternoon when circumstances permit	0	1	2	3
f. Sitting and talking to someone	0	1	2	3
g. Sitting quietly after a lunch without alcohol	0	1	2	3
h. In a car, while stopped for a few minutes in traffic	0	1	2	3 n.a.
n.a.: not applicable (not driving, children)	TOTAL:		/21 or 24	

4. *When did sleepiness start?* (approximate mnth/day/year) _____

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

MUSCLE WEAKNESS/CATAPLEXY SYMPTOMS
If treated with medications, you must answer questions as if you were untreated for any sleep disorder, unless specified otherwise. If completed by the parent of a younger child, answer as for the child.

5. *Have you or your child had episodes where you or your child's mouth suddenly opens or/and the tong protruded without any obvious reason?*

___NO ___YES: MORE THAN ONCE? ___NO ___YES:

6. *Have you or your child had episodes of muscle weakness or muscle paralysis (for example staggering or loopy gait, not able to stand on your legs leading to crumbling down slowly) hat occurred unexpectedly?*

___NO ___YES: MORE THAN ONCE? ___NO ___YES:

7. *Does anything unusual happen to you or your child when laughing or joking around?*

___NO ___YES: MORE THAN ONCE? ___NO ___YES:

8. *Did you or your child ever experience that your or his/her lower jaw was weakened during emotions, like laughing excitement, anger?*

___NO ___YES: MORE THAN ONCE? ___NO ___YES:

9. *Did you ever experience episodes of weakness in face, dropping of the jaw or head?*

___NO ___YES: MORE THAN ONCE? ___NO ___YES:

10. *Did you (or you child) experience episodes of muscle weakness in your/his or her legs or buckling of knees when having an emotion or without any reasons?*

___NO ___YES: MORE THAN ONCE? ___NO ___YES:

11. *Do you or your child experience feeling suddenly weak and without muscle strength?*

___NO ___YES: MORE THAN ONCE? ___NO ___YES:

Interviewer: if answered yes to questions 5-11 please continue, if not, skip ahead to question 15

12. *When did this symptom occur the first time?* (approximate month/day/year) _____

13. *How long does the muscle weakness typically last?*
□ < 5 seconds □ 5 seconds – 30 seconds □ 30 seconds – 2 minutes
□ 2 minutes – 10 minutes □ > 10 minutes

14. *How frequently do you experience one of these episodes of muscle weakness?*
□ Once, or more, per day □ Several times per week □ Once per week
□ Once per month □ Once per year, or less □ Never

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolepsy (DIGSAN) *continued*

OTHER NARCOLEPSY SYMPTOMS

If treated with medications, you must answer questions as if you were untreated for any sleep disorder, unless specified otherwise. If completed by the parent of a younger child, answer as for the child.

15. *Do or your child imagine feeling/seeing/hearing unusual and/or frightening people, animals, or objects, when you…*

	Never	**Rarely** Only a few times ever	**Infrequently** Less than once/month	**Sometimes** At least once/month, but less than once/week	**Often** At least once/week
a)…fall asleep abruptly?					
b)…wake up in the morning?					
c)…wake up during the night?					
d)…take a nap?					
e)…are drowsy?					

*If you responded "Never" to **ALL** of the situations in question 15 (a-e), please skip ahead to 17*

Please describe two of these events.

circumstance (a-e) _____

_____

circumstance (a-e) _____

_____

16. *When did you or your child experience one of these events the first time?* (approximate month/day/year)

_____

17. *How often do you or your child…*

	Never	**Rarely** Only a few times ever	**Infrequently** Less than once/month	**Sometimes** At least once/month, but less than once/week	**Often** At least once/week
a)…awaken in the morning and find that you are unable to move?					
b)…awaken from a nap and find that you are unable to move?					
c)…find that you are unable to move when falling asleep, either for the night or a nap?					

If you responded "Never" to **ALL** of the situations in question 17 (a-c), please skip to question 20

Please describe two of these events.

circumstance (a-e) _____

_____

circumstance (a-e) _____

_____

18. *Are these events frightening to you or your child?*

☐ Always ☐ Usually ☐ Often ☐ Rarely ☐ Never

19. *When did you or your child experience one of these events the first time?*(approximate month/day/year)

_____

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

DISTURBED SLEEP

If treated with medications, remember to answer questions as if you were untreated for any sleep disorder, unless specified otherwise. If completed by the parent of a younger child, answer as for the child.

20. *How often do you or your child have difficulty falling asleep at night?*
□ Always (every night) □ Usually (several times/week) □ Often (several times/month)
□ Rarely (several times/year) □ Never

21. *How often do you or your child sleep restlessly (moving a lot)?*
□ Always (every night) □ Usually (several times/week) □ Often (several times/month)
□ Rarely (several times/year) □ Never

22. *How often do you or your child talk during sleep?*
□ Always (every night) □ Usually (several times/week) □ Often (several times/month)
□ Rarely (several times/year) □ Never

23. *How often do you or your child wakes up in the middle of the night unable to go back to sleep?*
□ Always (every night) □ Usually (several times/week) □ Often (several times/month)
□ Rarely (several times/year) □ Never

24. *How often do you or your child dream excessively at night, having exhausting dreams for example?*
□ Always (every night) □ Usually (several times/week) □ Often (several times/month)
□ Rarely (several times/year) □ Never

OTHER

25. *Did you or your child loose or gained weight with the onset of this problem?*
□ Lost weight How much _____ in _____months
□ No change
□ Gained weight How much _____ in _____months

26. (if aplicable) *Did your sign show signed of premature puberty?*
□ Yes What age _____ What symptom_____

SLEEP TESTS

27. If you or your child had a nocturnal sleep study please report the following:
(approximate month/day/year) _____

Total sleep Time (hr)	
Nocturnal REM latency (min)	
Sleep Efficiency (%)	
Periodic Leg Movements Index (PLMI/hr)	
Apnea hypopnea Index (AHI/hr)	

28. If you or child had a Multiple Sleep latency test (MSLT) please report the following:
(approximate month/day/year) _____

	nap 1	nap 2	nap 3	nap 4	nap 5	mean
MSLT sleep latencies						
Presence of REM sleep						# SOREMP

Year of narcolepsy diagnosis:				

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

SECTION IV. MEDICAL HISTORY

INTERVIEWER: When information from medical records may be relevant to psychiatric condition, record physician name, hospital name, city, state, and treatment dates.

	No	Yes	Unk
1. *Have you ever had any serious physical illnesses or medical problems*? If yes, specify illness: _____ _____ _____	0	1	9
2. *Did you ever have, even transient, neurological problems as*			
Disorientation?	0	1	9
Memory deficits?	0	1	9
Epileptic seizures?	0	1	9
If yes, specify, was it preceded by a non-specific flu like illness with temperature, headache, fatigue, etc. _____ _____ _____			
3. *Have you had an MRI? Do you know the results*? _____ _____	0	1	9
4. *Have you had a lumbar punction (spinal tap) or any other biological test because of an encephalitis (brain inflamation or infection) was suspected?* _____ _____	0	1	9
5. *Are you taking any medications regularly (including aspirin and oral contraceptives)?*	0	1	9

Medication	Dosage per day	Duration of dosage Weeks
_____	_____	
_____	_____	
_____	_____	
_____	_____	

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolepsy (DIGSAN) *continued*

SECTION V. PSYCHOSIS INTERVIEW

I would like to read to you a list of experiences that other people have reported. Tell me which ones you have had.

INTERVIEWER: Record an example of each positive response in the margins (for each psychotic symptom, probe for description and chronology).

Has there been a time when…	No	Susp	Yes	Unk
1. *You heard voices? For example, some people have had the experience of hearing people's voices whispering or talking to them, even when no one was actually present.*	**0**	**1**	**2**	**9**
If yes,				
Did/Does it happen only when you fall asleep or just shortly after you wake up?	0	1	2	9
Did/Does it happen only when you are awake but very sleepy?	0	1	2	9
How do/did you explain it? _____				
Were/are you convinced that these voices were real?				
If yes,				
Did/Do you think the voices were real only immediately after it happened?	0	1	2	9
Did/Does the feeling that the voices were real lasted only for a few hours or days, and inside you knew it was just not possible to have occurred?	0	1	2	9
Are you still convinced that these voices were/are real?	0	1	2	9
Did you change your behavior as a result of the voices?	0	1	2	9
With regard to narcolepsy				
Did you start hearing voices before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplexy (weakness when laughing/joking) started*?				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did the voices appear only after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
2. *Did/do you have beliefs or ideas that others did not share or later found out were not true – like people being against you, people trying to harm you, or people talking about you?*	**0**	**1**	**2**	**9**
If yes, (record an example of these ideas in the margins)				
Did/Does it happen only when you fall asleep or just shortly after you wake up?	0	1	2	9
Did/Does it happen only when you are awake but very sleepy?	0	1	2	9
How do/did you explain it? _____				
At the time this occurred, were you convinced that these beliefs or ideas were real?	0	1	2	9
Are you still convinced that they are real now?	0	1	2	9
Did you change your behavior as a result of these beliefs or ideas?	0	1	2	9

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

		No	Susp	Yes	Unk
With regard to narcolepsy					
Did these beliefs or ideas started before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplexy (weakness when laughing/joking) first started*					9
How long before or after?	days [] weeks [] months [] years []				9
How often did they happen?	daily [] weekly [] monthly [] yearly []				9
How long did they last?	Hours [] days [] weeks [] months [] years []				9
Did these beliefs appear only after you started a narcolepsy treatment?		0	1	2	9
If yes, specify treatment _____					
Did these beliefs get reversed after you stop a narcolepsy treatment?		0	1	2	9
3. *Did/do you believe you were being given special messages (e.g. through the TV or the radio)?*		**0**	**1**	**2**	**9**
If yes, (record an example of these ideas in the margins).					
Did/Does it happen only when you fall asleep or just shortly after you wake up?		0	1	2	9
Did/Does it happen only when you are awake but very sleepy?		0	1	2	9
How do/did you explain it? _____					
At the time you received this message, were you convinced the message was real?		0	1	2	9
Are you still convinced that the message was special for you and real?		0	1	2	9
Did you change your behavior as a result of these messages?		0	1	2	9
With regard to narcolepsy					
Did you receiving these messages started before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplexy started?*					9
How long before or after?	days [] weeks [] months [] years []				9
How often did they happen?	daily [] weekly [] monthly [] yearly []				9
How long did they last?	Hours [] days [] weeks [] months [] years []				9
Did these beliefs appear only after you started a narcolepsy treatment?		0	1	2	9
If yes, specify treatment _____					
Did these beliefs get reversed after you stop a narcolepsy treatment?		0	1	2	9
4. *Did/do you believe that you had done something terrible for which you should be punished?*		**0**	**1**	**2**	**9**
If yes, (record an example of these ideas in the margins).					
Did/Does it happen only when you fall asleep or just shortly after you wake up?		0	1	2	9
Did/Does it happen only when you are awake but very sleepy?		0	1	2	9
How do/did you explain it? _____					
At the time it happened, were you convinced about it?		0	1	2	9
Are you still convinced now that you have done something terrible?		0	1	2	9
Did you change your behavior as a result of the belief?		0	1	2	9

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

	No	Susp	Yes	Unk
With regard to narcolepsy				
Did you receiving these messages started before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplex started?*				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did these beliefs appear only after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
Did these beliefs get reversed after you stop a narcolepsy treatment?	0	1	2	9
5. *Did/do you believe that you were especially important in some way, or that you had powers to do things that other people could not do?*	**0**	**1**	**2**	**9**
If yes, (record an example of these ideas in the margins).				
Did/Does it happen <u>only</u> when you fall asleep or just shortly after you wake up?	0	1	2	9
Did/Does it happen <u>only</u> when you are awake but very sleepy?	0	1	2	9
How do/did you explain it? _____				
Were you convinced about this only in the past?	0	1	2	9
Are you still convinced about this today?	0	1	2	9
Did you change your behavior as a result of these beliefs or ideas?	0	1	2	9
With regard to narcolepsy				
Did this belief first start before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplex started?*				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did these beliefs appear only after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
Did these beliefs get reversed after you stop the narcolepsy treatment?	0	1	2	9
6. *Did/do you had the feeling that you were under control of some force or power other tan yourself?*	**0**	**1**	**2**	**9**
If yes, (record an example of these ideas in the margins).				
Did/Does it happen <u>only</u> when you fall asleep or just shortly after you wake up?	0	1	2	9
Did/Does it happen <u>only</u> when you are awake but very sleepy?	0	1	2	9
How do/did you explain it? _____				
Were you convinced about this only in the past?	0	1	2	9
Are you still convinced you are under control?	0	1	2	9
Did you change your behavior as a result of these feelings?	0	1	2	9

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

	No	Susp	Yes	Unk
With regard to narcolepsy				
Did the feeling appear of being under control start before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplex started?*				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did these feelings appear only after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
Did these beliefs get reversed after you stop the narcolepsy treatment?	0	1	2	9
7. *Did/do you feel that you suffered a change in your body or in your physical appearance that others could not see?*	**0**	**1**	**2**	**9**
If yes, (record an example of these ideas in the margins).				
Did/Does it happen only when you fall asleep or just shortly after you wake up?	0	1	2	9
Did/Does it happen only when you are awake but very sleepy?	0	1	2	9
How do/did you explain it? _____				
Were you convinced about this only in the past?	0	1	2	9
Are you still convinced that your appearance has changed?	0	1	2	9
Did you change your behavior as a result of this change of appearance?	0	1	2	9
With regard to narcolepsy				
Did the feeling appear of being under control start before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplexy started?*				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did these feelings appear only after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
Did these beliefs get reversed after you stop the narcolepsy treatment?	0	1	2	9
8. *Have you ever engaged in any unusual behavior, had speech that was mixed up or did not make sense to other people?*	**0**	**1**	**2**	**9**
If yes, (record an example of these behaviors in the margins).				
Did/Does it occur only in the middle of the night?	0	1	2	9
Did/Does it occur only when you are awake during the day but very sleepy or tired?	0	1	2	9
How do/did you explain it? _____				

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

	No	Susp	Yes	Unk
With regard to narcolepsy				
Did it start to happen before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplex started?*				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did this unusual behavior or speech appear after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
Did these behaviors get reversed after you stop the narcolepsy treatment?	0	1	2	9
9. *Had your body ever stuck in one position so that you could not move?*	**0**	**1**	**2**	**9**
If yes, (record an example of these behaviors in the margins).				
Did/Does it happen <u>only</u> when you fall asleep and/or shortly after you wake up?	0	1	2	9
Did/Does it happen <u>only</u> in the middle of a napo r when sleeping at night?	0	1	2	9
How do/did you explain it? _____				
With regard to narcolepsy				
Did it start to happen before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplex started?*				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did these behaviors appear after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
Did these behaviors get reversed after you stop the narcolepsy treatment?	0	1	2	9
10. *Have you experienced to have no emotions or have inappropriate emotions?*	**0**	**1**	**2**	**9**
Interviewer: record an example of these symptoms in the margins (probe for description and chronology).				
If yes				
Did this symptom start before [] after [] or at the same time [] *narcolepsy symptoms such as sleepiness or cataplex started?*				9
How long before or after? days [] weeks [] months [] years []				9
How often did they happen? daily [] weekly [] monthly [] yearly []				9
How long did they last? Hours [] days [] weeks [] months [] years []				9
Did these symptoms appear after you started a narcolepsy treatment?	0	1	2	9
If yes, specify treatment _____				
Did these symptoms get reversed after you stop the narcolepsy treatment?	0	1	2	9
Were these symptoms related to a depressive or manic mood episode?	0	1	2	9

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

INTERVIEWER: If yes, complete the following questions about mood

Now, I'm going to ask you some questions about your mood.

	No	Susp	Yes	Unk
1.				
1.a) *Have you ever had a period of at least one week when you were bothered most of the day, nearly every day, by feeling depressed, sad, down, low?*	0	1	2	9
1.b) *By feeling irritable?*	0	1	2	9
1.c) *By feeling anxious?*	0	1	2	9
1.d.) *Have you ever had a period of at least one week when you did not enjoy most things* even things you usually liked to do?	0	1	2	9

INTERVIEWER: Do you suspect a past or current DEPRESSIVE episode from subject's responses, behavior, or other information? **0 1 2 9**

If yes, specify:

_____

_____

2.				
2.a) *Have you ever had a period when you felt extremely good or high, clearly different from your normal self? (Was this more than just feeling good?*	0	1	2	9
2.b) *Did you ever had a period when you were unusually irritable, clearly different from your normal self so that you would shout at people or start fights or arguments?*	0	1	2	9
2.c) *Have you ever had periods lasting even a day or two when you felt unusually cheerful,* irritable, energetic or hyper*?*	0	1	2	9
2.d.) *Have there been times when you felt much more energetic than usual and needed* less sleep than usual?	0	1	2	9

INTERVIEWER: probe for additional symptoms if necessary, using additional probes.
(e.g. Did you experience racing thoughts of pressure to keep talking? Were you over-confident? Did you make unrealistic plans? Were you uncharacteristically impulsive? Did you experience increased activity or increased talkativeness? Gather and record information on any (even mild) mood states that seem qualitatively different from a normal good mood and that indicate hypomania. Record response including subject's description of the mood below:

_____

_____

_____

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

	No	Susp	Yes	Unk
If any yes to questions 2ª-d: *Did this last persistently throughout the day or Intermittently for two days or more?*				
INTERVIEWER: Do you suspect a past or current MANIC episode from subject's responses, behavior, or other information? If yes, specify: _____ _____	**0**	**1**	**2**	**9**
INTERVIEWER: If the subject has/had psychotic symptoms as well as mood Symptoms, complete the following questions about temporal relationship between mood alteration and psychotic symptoms.				
3.				
3.a) *Did the voices, visions or beliefs occur either just before the depression and/or manic episode or after it cleared?*	0	1	2	9
If yes: *How long were they present before the depression/mania began*? _____Days *How long did they last after your mood returned to normal*? _____Days				
3.b) *Was there ever a period of time when you had (psychotic symptoms) when you were not feeling (depressed/high or excited*)?	0	1	2	9
If yes: *Did these symptoms ever last as long as one week while you were not (depressed/high*)?	0	1	2	9
How long did you have these symptoms when you were not (depressed/high)? _____Days _____Weeks				
INTERVIEWER: Record an example of each positive response in the margins.				
11. Does the patient present affective flattening, poverty of speech during the interview?	0	1	2	9
12. Is the patient currently exhibiting signs of incoherence? (not related to sleep or dreaming)	0	1	2	9
13. Is the patient currently exhibiting disorganized thinking? (not related to sleep or dreaming)	0	1	2	9
14. Is the patient currently exhibiting bizarre ideas? (not related to sleep or dreaming)	0	1	2	9
13. Is the patient currently exhibiting a disgressive or over elaborate speech or marked loosening of associations?	0	1	2	9

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

SLEEP DISORDER INTERVIEWER: IF YOU SUSPECT A PSYCHOTIC OR MOOD DISORDER, PLEASE REFER TO SPECIALIST IN PSYCHIATRY TO COMPLETE DIAGNOSIS.

SLEEP DISORDER INTERVIEWER: If in your opinion, the patient only has narcolepsy and that all his/her symptoms can be explained by it, please rate narcolepsy only below.

PSYCHIATRIST INTERVIEWER: If in your opinion, the patient only has schizophrenia or a delusional disorder and that all his/her symptoms can be explained by it, please rate the corresponding single diagnosis below.

ADJUDICATION: In case of a dual diagnosis, both narcolepsy and psychotic disorder like Schizophrenia or a mood disorder are present, please have the opinion of both a psychiatrist and a sleep specialist to fill up the information below.

INTERVIEWER: In your opinion, the subject has: (circle what applies)

Narcolepsy only	[]
Narcolepsy + Schizophrenia	[]
Narcolepsy + Delusional disorder	[]
Narcolepsy + Bipolar disorder	[]
Narcolepsy + Schizoaffective disorder	[]
Narcolepsy + Psychosis (not specified)	[]

Describe: _____

Schizophrenia alone	[]
Delusional disorder alone	[]
Bipolar disorder	[]
Schizoaffective disorder	[]
Psychosis (not specified)	[]

Describe: _____

If 2 diagnoses, did these conditions started at the same time []
or independently/separately [] ?

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

*__Schizophrenia__: according to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), to be diagnosed with schizophrenia, three diagnostic criteria must be met:
Characteristic symptoms: two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).
Delusions
Hallucinations
Disorganized speech, which is a manifestation of formal thought disorder
Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior
Negative symptoms: blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)
If the delusions are judged to be bizarre, or hallucinations consist on hearing one voice participating in a running commentary of the patient's actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.
Social or occupational dysfunction: for a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.
Significant duration: continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).
If signs of disturbance are present for more than a month but less than six months, the diagnosis of schizophreniform disorder is applied.

***Delusional disorder**: It is a stable disorder characterized by the presence of delusions to which the patient clings with extraordinary tenacity. The illness is chronic and frequently lifelong. The delusions are logically constructed and internally consistent. The delusions do not interfere with general logical reasoning (although within the delusional system the logic is perverted) and there is usually no general disturbance of behavior. If disturbed behavior does occur, it is directly related to the delusional beliefs.
The individual experiences a heightened sense of self-reference. Events which, to others, are non significant are of enormous significance to him or her, and the atmosphere surrounding the delusions is highly charged.
Diagnosis of a specific type of delusional disorder can sometimes be made based on the content of the delusions. The Diagnostic and Statistical Manual of Mental Disorders (DSM) enumerates seven types:
Erotomanic type (erotomania)
Grandiose type
Jealous type
Persecutory type
Somatic type
Mixed type
Unspecified type

*__Bipolar disorder:__ is a condition in which people experience abnormally elevated (manic or hypomanic) mood states, to a degree that interferes with the functions of ordinary life. Many people with bipolar disorder also experience periods of depressed mood, There is no simple physiological test to confirm the disorder. Diagnosing bipolar disorder is often difficult, even for mental health professionals. In particular, it can be difficult to distinguish depression caused by bipolar disorder from pure unipolar depression. The younger the age of onset, the more likely the first few episodes are to be depressive.
Diagnostic of Bipolar disorder requires a manic or hypomanic episode, many patients are initially diagnosed and treated as having major depression.

***Schizoaffective disorder:** is a psychiatric diagnosis that describes a mental disorder characterized by recurring abnormal mood and psychotic components. The mood component may be elevated or depressed (bipolar or depressive subtype), or simultaneously elevated and depressed (mixed episode), and these abnormal mood components alternate with, or occur together with distortions in perception. For a diagnosis of schizoaffective disorder to be valid, according to current DSM criteria (but not ICD criteria), there must be a period of at least two weeks of psychosis without mood disorder, and these symptoms cannot be due to medication(s), substance use or another medical condition.

continues

Diagnostic Interview for Genetic Studies Adapted for Narcolespy (DIGSAN) *continued*

***Narcolepsy:** is a disorder characterized by severe sleepiness and cataplexy (loss of muscle function in legs, face, or whole body when laughing or joking; the patient is awake but paralyzed or weak). Sleep paralysis is the temporary inability to talk or move when waking up (or when falling asleep). Hypnagogic hallucinations are vivid, often frightening, dreamlike experiences that occur while dozing, falling asleep and/or while awakening. Insomnia and vivid dreaming is also common.