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## Isolated global amnesia associated with autoimmune thyroid disease

Alan Jacobs, MD; James Root, PhD; and Wilfred Van Gorp, PhD

One week after developing a gastrointestinal illness, a 32-year-old man with a 15-year history of Hashimoto thyroiditis, with no previous cognitive or comportment changes, presented with confusion and extreme forgetfulness over 3 days. He repeated himself in conversations and lost memories from his recent past. There were no headaches, fevers, seizures, or focal elementary neurologic or systemic symptoms or signs. His judgment, personality, language, and reasoning abilities remained normal by history and mental status testing. Brain MRI on day 3 of his amnesia, with and without gadolinium, was normal. An EEG 3 weeks later was also normal. Ten days later, tests for antinuclear and anti-Hu antibodies were negative, CSF leukocyte count was 3/mm<sup>3</sup>, protein concentration was 20 mg/dL, and viral and bacterial cultures were negative. At this time, the serum thyroid peroxidase antibody concentration was 1,860 IU/mL (reference range, 0.0 to 2.0 IU/mL). Based on these data, a diagnosis of Hashimoto encephalopathy<sup>1</sup> was made.

Neuropsychological testing was conducted 2 weeks after the onset of his amnesia and revealed a highly focal and dense retrograde and anterograde amnesia in the context of only mild psychomotor slowing and visuospatial weakness. On measures of learning and memory, total forgetting was exhibited at 20 to 30 minutes, with evidence of forgetting occurring within several seconds following intact registration. All measures of recall, cued recall, and recognition were equally impaired (1st percentile). Remaining areas were all within the high average to very superior range and unaffected. [<sup>18</sup>F]Fluorodeoxyglucose PET, obtained 20 days later, revealed decreased glucose metabolism in bilateral temporal regions (figure).

After 5 weeks of persistent, severe amnesia, glucocorticoid therapy with prednisone 80 mg/day was started, and his memory dramatically improved over 1 week. The next week follow-up thyroid peroxidase antibody concentration was 800 IU/mL. Two weeks after that, while on 65 mg/day of prednisone, mental status testing found him fully oriented to time and place, performing normally on verbal and nonverbal tests of anterograde memory. His recollection of events over the 2 months preceding the onset of his amnesia was almost totally complete. He was back at work performing normally and tapered off the steroids over the next 2 months without further problems.

Follow-up neuropsychological examination was conducted 1.5 years later and was limited to domains that were areas of weakness on initial assessment. Results revealed dramatic improvements across all areas of learning and memory. Current memory performance did, however, remain lower than expected relative to general intellectual abilities.

**Discussion.** Our patient had the clinical syndrome of isolated global amnesia documented via mental status examination and formal neuropsychological testing. The underlying bilateral lesions in the temporal lobes were documented on [<sup>18</sup>F]fluorodeoxyglucose PET imaging, but no structural correlates were found on MRI and no electrophysiologic correlates were found on EEG. Moreover, CSF did not show overt signs of inflammation or infection. However, his high serum titers of thyroid peroxidase antibodies, combined with his response to steroids with a 1- to 2-week

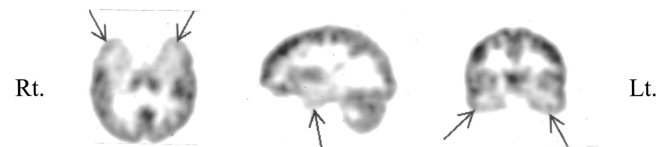


Figure. Brain PET using [<sup>18</sup>F]fluorodeoxyglucose obtained 40 minutes after the injection. Axial, sagittal, and coronal images demonstrate decreased glucose metabolism in bilateral temporal regions (arrows).

normalization of his previously stable, severe amnesia, establishes his syndrome as an “isolated global amnesia associated with autoimmune thyroid disease.”

A previous study described an amnesic syndrome in Hashimoto encephalopathy,<sup>2</sup> but the patient presented with a subacute confusional state, headaches, seizures, and myoclonus and there were mesial temporal lobe foci of T2 hyperintensity and T1 hypointensity on MRI. Moreover, despite some clinical improvement with steroid therapy, the severe amnesia and localized MRI abnormalities persisted. Another case of Hashimoto encephalopathy with reversible amnesia in the title<sup>3</sup> described a patient presenting with generalized seizures and postictal amnesia, along with fluctuating levels of confusion, flat affect, and recurrent seizures. Regarding the functional, but not structural, brain imaging findings in our case, a case of thyrotoxic autoimmune encephalopathy has been reported<sup>4</sup> in which MRI was normal but brain PET showed diffuse, multifocal hypometabolism that normalized upon patient recovery. Regarding the normal EEG findings in our case, it has been reported<sup>5</sup> that EEG findings reflect the severity of the underlying encephalopathy, indicating the relatively mild and restricted nature of our case. This case expands the spectrum of findings of Hashimoto encephalopathy.

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## SCN1A (2528delG) novel truncating mutation with benign outcome of severe myoclonic epilepsy of infancy

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The epileptic syndrome related to mutations in the *SCN1A* gene includes benign febrile seizures (FS), the more variable phenotype FS+, and severe myoclonic epilepsy in infancy (SMEI) or Dravet syndrome, one of the most severe types of infant epilepsy, which is resistant to drugs.<sup>1</sup> The clinical spectrum related to mutations of the *SCN1A* gene (chromosome 2q) has been divided according to the type of seizure and CNS impairment into four categories from the lightest (benign FS) to the most severe (classic type SMEI).<sup>2</sup> Evidence suggests that a severe disturbance of the function of the *SCN1A* gene is a major cause of SMEI, and that FS, FS+ (even with other types of seizures), and the milder and classic types of SMEI form a continuum of mutations in the  $\alpha$  subunit of *SCN1A*. Severe de novo mutations, such as truncating mutations, have been reported in SMEI.<sup>2,3</sup> We report a patient with SMEI with a benign outcome, in whom the clinical picture changed from SMEI in infancy to FS+ in adolescence and was associated with a novel, de novo truncating mutation of the *SCN1A* gene.

**Clinical report.** The patient was a 13-year-old boy with an IQ of 125 (Wechsler Intelligence Scale for Children-Revised). The family history was negative. At the ages of 6, 10, and 13 months, he had prolonged FS that lasted about 20 minutes. The EEG was normal. Phenobarbital (3 mg/kg/day) was given. Starting at the age of 18 months, afebrile complex partial seizures (CPS) with secondary generalization appeared monthly, on average. At the age of 2 years and 2 months and 2 years and 8 months, he presented in another hospital with two episodes of status epilepticus, one febrile and one afebrile. From ages 2 to 3, serial EEGs showed either focal spike activity (figure, A), bilateral frontal slowing, or diffuse polyspike waves accompanied by myoclonic jerks (figure, B). A brain interictal SPECT showed decreased perfusion in the right temporal and right frontal lobes (for more details, see figure E-1 on the *Neurology* Web site; go to [www.neurology.org](http://www.neurology.org)). The karyotype, biochemical and metabolic evaluation (for more details, see Appendix E-1), and MRI were normal. Because the afebrile seizures were present daily, all major antiepileptic drugs, including adrenocorticotropic hormone, were tried in full dosage but were unable to control the seizures. From age 4, in therapy with valproate and vigabatrin, the frequency of seizures gradually decreased. At age 9 years and 5 months, during a long-term video EEG monitoring 4 days after stopping valproate therapy was discontinued abruptly. The EEG background was completely normal (figure, C). The patient devel-

oped CPS with secondary generalization starting in the right temporal region, which lasted 2 minutes (figure, D). At age 13, in therapy with valproate, the patient experienced a similar FS (for more details about the drug used, dosage, and effects, see Appendix E-2). A mutational analysis for the *SCN1A* gene was then performed.<sup>4</sup> Molecular analysis detected a c.2528delG in the patient's DNA sample. The nucleotide change, which lies within exon 14 and has not been described previously, is predicted to lead to a frame shift after the amino acid 842 residue (out-of-frame deletion) and premature termination at 853 (Gly842fsX853). The molecular analysis of the patient's parents' DNA detected normal alleles, suggesting that the mutation arose de novo.

**Discussion.** We report a case of SMEI and a favorable clinical outcome, in which we identified a novel truncating mutation (2528delG) of the *SCN1A* gene. As the boy matured from infancy to adolescence, his seizures progressively changed from SMEI to FS+ controlled by drug therapy. This is the first report of a mutation predicted to generate a premature stop codon (i.e., a loss-of-function mutation) associated with a benign outcome of SMEI. The diagnosis of SMEI was justified by the presence of prolonged FS that included recurrent status epilepticus and frequent and different types of afebrile seizures, including myoclonic seizures, which were resistant to all major antiepileptic drugs.<sup>1,2</sup> The absence of mental retardation can be attributed to the reduction in the frequency of seizures because of therapy after the age of 4 years.<sup>2</sup> In some cases, mental retardation can be very mild, and the diagnosis of SMEI does not depend on the presence or absence of a single clinical sign.<sup>2,3</sup> Moreover, truncating mutations are usually found in SMEI.<sup>2,3</sup> We acknowledge that the presentation of a single case is not sufficient to draw general statements on the issue. The clinical implication of our report is that carriers of devastating ion-channel mutations do not necessarily have a poor prognosis.<sup>5</sup> This may be important in disease management and treatment, because the clinical picture may improve in some cases to the point that the patient is able to lead a normal life.

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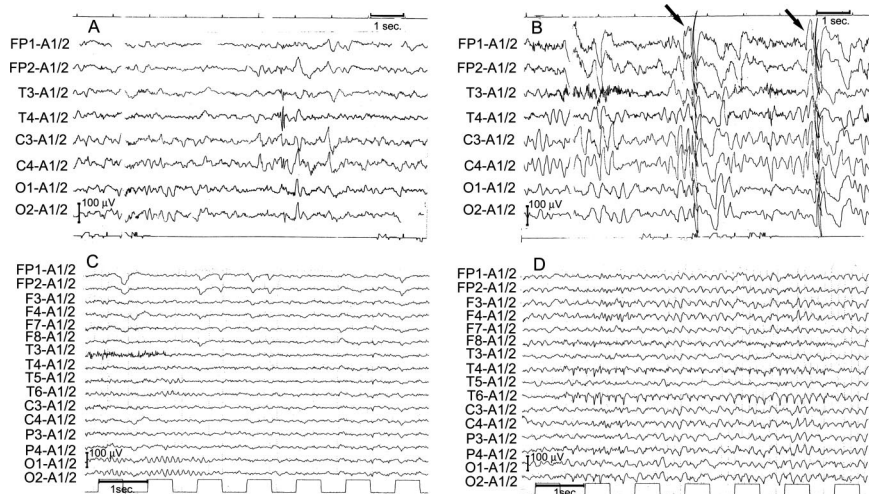


Figure. EEGs from the patient. EEGs at the age of 2 years showing normal background activity with sporadic right temporal fast spikes (A) and at 3 years myoclonic jerks (B, arrows). At age 9 years and 5 months, a long-term video EEG monitoring 4 days after stopping valproate showed one normal background activity following by a seizure consisting of turning the head to the left side, extension, and hypertonia of the left arm, emission of guttural noises, and generalized rhythmic jerks lasting about 2 minutes (C). Note the initial bioelectrical correlate consisting of temporal (posterior) sharp theta activity (D).

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## Preimplantation exclusion of embryos at risk for prion diseases

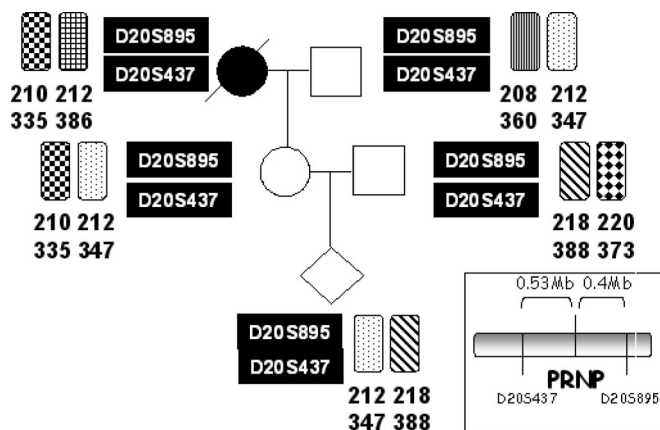
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Approximately 15% of human prion diseases are inherited disorders associated with *PRNP* gene mutations, such as familial Creutzfeldt–Jakob disease (fCJD). fCJD, a dominant late-onset neurodegenerative disorder with near 100% penetrance, is prevalent among Jews of Libyan descent having a common *PRNP* E200K founder mutation.<sup>1</sup> Mutation analysis can be used for diagnostic or predictive (presymptomatic) genetic testing in affected families. Offspring of affected individuals have a 50% chance of expressing the disorder; nevertheless, the age at onset varies between individuals.

Many patients at risk for fCJD prefer not to know their genetic status but still do not want to pass on the mutation, if it exists, to their children. Prenatal diagnosis through direct mutation analysis forces them to learn their own carrier status. A partial resolution for such problem was introduced by exclusion prenatal testing in which the fetus is tested for the presence of either allele of the relevant gene from the affected grandparent.<sup>2</sup> This procedure is designed to avoid the birth of at-risk offspring to an individual who chose not to perform a predictive test. A major drawback of exclusion testing is that couples at risk for fCJD are exposed to moral and ethical dilemmas of terminating pregnancy of unaffected fetuses. This problem may be circumvented by preimplantation genetic diagnosis (PGD).<sup>3</sup>

We report the results of exclusion PGD for fCJD. A 34-year-old woman was referred to the clinic following the death of her 55-year-old mother from fCJD associated with E200K *PRNP* mutation. She did not wish to learn her carrier status, yet sought to have children who were not mutation carriers. PGD cycle was performed using standard GnRH agonist administration, and oocyte fertilization carried out by intracytoplasmic sperm injection. Following embryo biopsy, DNA was extracted from the retrieved cells for PCR analysis. Exclusion genetic testing was performed by genotyping for *PRNP* flanking markers, D20S895 and D20S437, at a distance of 0.4 and 0.53Mb (figure). Haplotypes were constructed based on DNA obtained from the referred couple and the at-risk woman's parents, and embryos were classified according to whether they inherited *PRNP* haplotype from the at-risk woman's mother or father. There was no risk for allele dropout as a potential source for false negative as the utilized markers were fully informative. Whereas embryos with the woman's mother's haplotype had a 50% chance of carrying an E200K mutation, embryos with the woman's father's haplotype were undoubtedly mutation-free. Two unaffected embryos were transferred back and resulted in a successful singleton pregnancy for which amniocentesis validated the exclusion PGD.

In fCJD, similar to Huntington disease (HD),<sup>4</sup> voluntary predictive testing is infrequent owing to the reluctance of at-risk individuals to cope with the burden of presymptomatic knowledge. Previously we offered prenatal exclusion testing for such individuals at risk for fCJD. This method, however, had adverse aspects such as aborting unaffected fetuses. Moreover, if, following exclusion testing showing a possible affected fetus, the couple opted to continue the pregnancy, the future child's autonomy would be breached because he would not have any choice in the decision whether to be tested; and once his at-risk parent developed fCJD, this child would definitely become a carrier for the disorder.



*Figure. Pedigree of family with familial Creutzfeldt–Jakob disease. For each individual in the pedigree, circle = woman; square = men; filled black circle with oblique line = deceased affected woman; diamond = unborn child. Examples of the genetic profiles obtained for every analyzed individual are given in black insets with the respective marker (i.e., D20S895 and D20S437). Following the construction of haplotypes, each rounded rectangle represents a haplotype with a distinct pattern shown for clarity. The “black dots” haplotype in the embryo segregated from the nonaffected grandfather and the “checkerboard” haplotype in the pregnant woman was inherited from her affected mother. It is unknown whether the E200K mutation in the *PRNP* gene is linked to the “checkerboard” or to the “small grid” haplotype of the affected grandmother. (Inset) *PRNP* locus and the distribution of the markers used in this study.*

Exclusion PGD, as was previously introduced for HD,<sup>5</sup> resolves these problems and offers a unique solution for familial prion diseases. An alternative, less desired option for such couples is “nondisclosure PGD” where only embryos that do not carry the mutation are selected for transfer and the results concerning the parents' carrier status are not disclosed to the couple at their request. This procedure is far from ideal because if all the embryos are affected, the absence of a transfer would imply that the parent is also affected; the treating staff would be required to simulate transfer to preserve the couple's wish not to know.

Certain points should be considered prior to wide implementation of exclusion PGD for fCJD. In case that at-risk person is actually not a mutation carrier, half of the embryos that inherited a haplotype from the affected parent of this person would be noneligible for transfer and surplus healthy embryos would be erroneously discarded. There are financial drawbacks that need to be raised as the cost of PGD is only justified by the wish of the parents to avoid knowing their genetic status. However, by implementing exclusion PGD, the increasing number of at-risk families may be able to halt the transmission of this devastating, nontreatable disease and to avoid ethical dilemmas concerning predictive testing.

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## REM sleep behavioral disorder in pure autonomic failure (PAF)

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Pure autonomic failure (PAF) is an idiopathic sporadic disorder characterized by orthostatic hypotension with evidence of more widespread autonomic failure. It has been suggested that PAF belongs to the group of synucleinopathies, as autopsy studies showed  $\alpha$ -synuclein-positive Lewy bodies in sympathetic neurons of patients with PAF.<sup>1</sup> REM sleep behavioral disorder (RBD) appears to be an almost universal feature of synucleinopathies. Whereas initial studies suggested that RBD specifically occurs in multiple system atrophy (MSA), subsequent studies showed that it is also a frequent feature of Parkinson disease (PD) and dementia with Lewy bodies (DLB).<sup>2</sup> Furthermore, patients with isolated RBD often later develop PD.<sup>3</sup>

We here present a consecutive unselected series of three patients with PAF (M/F: 2/1, age: 52 to 74 years) with a disease duration of 3, 7, and 7 years. In all, bed partners reported nocturnal symptoms of RBD (table). History of RBD was typical with vigorous sleep-related motor behaviors, usually accompanying vivid striking dreams. All patients underwent neurologic examination, autonomic testing, standard structural brain MRI, cardiac scintigraphy with [<sup>123</sup>I]metaiodobenzylguanidine (MIBG), and 2 consecutive nights of standard 8-hour videopolysomnography in a digital sleep laboratory. Serum norepinephrine levels were measured in two of the patients. Blood was taken after 30 minutes of supine rest and after 3 minutes in standing position.

All patients showed a lack of sympathetic response in autonomic testing and described further symptoms of autonomic failure, whereas neurologic examination did not show parkinsonism (see table). Also the structural brain MRI gave normal results in all cases. MIBG scintigraphy demonstrated abnormally reduced cardiac tracer uptake, indicating postganglionic sympathetic denervation typical for PAF. Supine norepinephrine levels were low

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in both patients and increased only slightly in standing position (see table). The values were in the range as reported for PAF.<sup>4</sup> Videopolysomnography revealed typical features of RBD with intermittent absence of muscle atonia during REM sleep in all patients. These episodes were accompanied by simple and complex motor behaviors like twitching and beating; sleep-talking was additionally observed in one patient. A moderate sleep apnea syndrome was present in one patient.

This is the first report of RBD in PAF. As the diagnosis of PAF was made clinically, we cannot exclude that the patients may develop MSA in the future. However, the diagnosis of PAF is supported by clinical presentation, normal MRI, low serum norepinephrine levels,<sup>4</sup> and reduced cardiac tracer uptake in MIBG scintigraphy. MIBG scintigraphy differentiates MSA from other conditions, mainly PD, with an overall sensitivity of 89.7% and a specificity of 94.6%.<sup>5</sup> Our data on the presence of RBD in PAF are at variance with an earlier study that did not find RBD in six PAF patients.<sup>6</sup> The discrepancy is best explained by the assumption that RBD is a possible but not a necessary phenomenon in PAF.

As RBD is due to brainstem dysfunction, demonstration of RBD provides evidence for CNS involvement in our patients. A recent study reported that PAF patients may develop PD or DLB years after onset of autonomic failure,<sup>7</sup> suggesting a spread of the degeneration in PAF to the CNS. In addition, many PD and DLB patients have autonomic failure due to degeneration of postganglionic sympathetic neurons, as in PAF. These observations together with the presence of  $\alpha$ -synuclein-positive Lewy bodies are compatible with the assumption that the synucleinopathies including PAF, PD, and DLB form a clinical and pathologic spectrum rather than represent clearly distinguishable disease entities.

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Table Patient characteristics

	Patient 1	Patient 2	Patient 3
Sex	M	M	F
Age, y	71	52	74
Disease duration, y	3	7	7
Neurologic examination	Hoarseness, slightly reduced arm swing (not reproduced at follow-up)	Normal	Essential tremor
Drop of systolic blood pressure after standing (3 min), mm Hg	101	80	50
Structural brain MRI	Normal results	Normal results	Vascular lesions of white matter
MIBG scintigraphy	Reduced cardiac tracer uptake	Reduced cardiac tracer uptake	Reduced cardiac tracer uptake
Serum norepinephrine levels	114.6 ng/L (supine), 169.3 ng/L (standing)	10.0 ng/L (supine), 19.7 ng/L (standing)	Not done
Videopolysomnography	RBD	RBD, periodic complex motor behaviors	RBD, moderate sleep apnea syndrome

MIBG = [<sup>123</sup>I]metaiodobenzylguanidine; RBD = REM sleep behavioral disorder.

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## VIDEO

## Continuous positive airway pressure as treatment for catathrenia (nocturnal groaning)

J. Iriarte, MD; M. Alegre, MD; E. Urrestarazu, MD; C. Viteri, MD; J. Arcocha, MD; and J. Artieda, MD

Nocturnal groaning (catathrenia; from the Greek words kata = below, under; threnia = to lament) is a new sleep disorder included in the recent International Classification.<sup>1</sup> Few cases have been reported, and there is no treatment currently available.<sup>2–6</sup> We present a patient producing tremendous noises during sleep. She did not have any other remarkable disease. At admission to our hospital for a polysomnography, she was 62 years old. She reported that this phenomenon started many years ago. She was sent for the study because the noise was very disturbing to her family. Her neurologic and otorhinolaryngologic exams (including a full laryngoscopic exam) were normal. The patient did not express any subjective complaint except for a sporadic dry mouth in the morning. The subjective quality of her sleep was very good. The standard polysomnographic recording included EEG, electro-oculogram, oxygen saturation, airflow, respiratory band, electromyography in anterior tibialis, and EKG. For the recording of video and audio, we used a regular camera (we did not use a snoring sensor because we do not use it on a regular basis, and we used the audio from the video camera). A few minutes after the beginning of sleep, she started producing these noises. The camera recorded an expiratory waxing and waning periodic groaning noise with an irregular movement of the abdominal wall (see the video on the *Neurology* Web site; go to [www.neurology.org](http://www.neurology.org)). This occurred during the entire night independently of the sleep stage and body position. The polysomnography confirmed a respiratory dysrhythmia in all sleep stages (figure, stages 2, 4, REM; see page 610), with frequent oxygen desaturations disproportionate to the expected values for a mild obstructive sleep apnea disorder with predominance of obstructive hypopneas more than apneas (index of apnea-hypopnea [IAH]: 16, desaturation index: 50, minimum oxygen saturation: 79%) (figure, baseline). We discussed with the patient and the family the possibility of a trial with continuous positive airway pressure (CPAP), considering that a continuous positive pressure might keep the glottis open and lead to a decrease in the noise. The patient and the family approved the trial. During the night, with use of CPAP (6 cm H<sub>2</sub>O), the noise disappeared almost completely. She tolerated the CPAP perfectly, and she was asymptomatic the next morning. The respiratory rhythm became normal (figure, CPAP-2), but the oxygen saturation was still a little low (IAH: 11, desaturation index: 11, minimum oxygen saturation: 82%) (figure, CPAP).

Catathrenia is described as a syndrome with expiratory groaning associated with a respiratory dysrhythmia.<sup>1,4</sup> This disorder is accompanied by an expiratory noise, like a groaning, normally more frequent in REM sleep but also in stages 1 and 2. The predilection for REM sleep might be related to an abnormal asynchronous activation of the diaphragm and the oropharyngeal muscles in this sleep stage. As in our patient, the physical, neurologic, and otorhinolaryngologic exams were normal in all cases. The noise appeared in clusters during the sleep, and it was not related to the body position. All cases started before the age of 36 years. Our patient has similar characteristics, and her case fulfills the diagnostic criteria for catathrenia. The differential diagnosis includes sleep talking, snoring, laryngospasm, stridor, nocturnal asthma, and moaning in epileptic seizures.<sup>1</sup>

Sleep talking is not periodic and sounds like a regular voice. Sleep-related laryngospasm is accompanied by a feeling of anxiety, breathing difficulties, and awakening of the patient. Nocturnal asthma and seizures are very different. Stridor is mainly inspiratory, it sounds different, and it does not occur in prolonged expiration. Snoring is an inspiratory phenomenon, and its mechanism is different. Snoring is supraglottic, whereas stridor is a glottic disorder. However, the characteristics of the sound in catathrenia suggest a subglottic mechanism.<sup>2,4</sup> In the previous reports, no treatment was suggested. In two patients described previously, the CPAP improved both the noise and the snoring, but only in one of them did the catathrenia sound decrease.<sup>4</sup> It is clear that this is a benign, non-life-threatening process, but in our case, the situation was almost hopeless, and the benefit with CPAP was dramatic.

In conclusion, our case supports the inclusion of catathrenia as a peculiar sleep disorder. As in other reports, the presence of a mild sleep apnea does not discard the diagnosis of catathrenia.<sup>2,4,6</sup> The other important question is the treatment, as suggested in the International Classification.<sup>1</sup> We think that CPAP can be an option for the treatment of this infrequent but sometimes very disabling sleep disorder.

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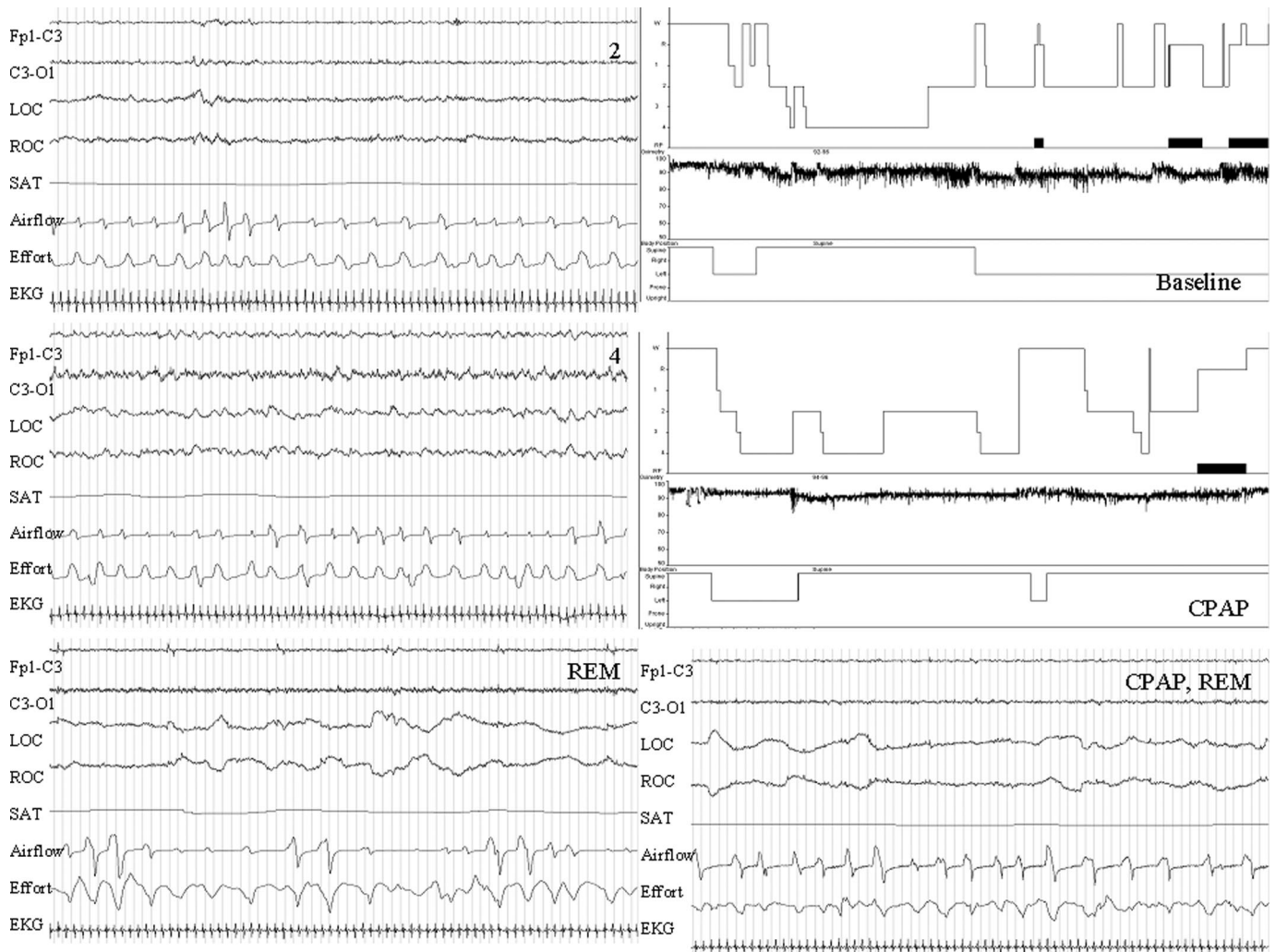


Figure. (Left) Three pages of the baseline polysomnography, in stage 2, stage 4, and REM. (Right) Hypnogram, oxygen saturation, and body position of the baseline study (baseline) and of the night with continuous positive airway pressure (CPAP). (Below) A page of the polysomnography of the night with CPAP in REM (CPAP-REM). LOC = left electro-oculogram; ROC = right electro-oculogram; Effort = thoracoabdominal band; RP = REM period; W = wakefulness; R = REM.

## Preservation of episodic musical memory in a pianist with Alzheimer disease

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Creativity is distinct from other brain activities. Little is known about the neural networks of music perception and musical memory.<sup>1</sup> However, there are reports that suggest that they may be subserved by distinct neural networks. This distinction is further explored through studying music perception in all its complexities, including pitch, timbre, rhythm, and harmony. Each of these perceptions may be differentially lateralized and further differentiated among musicians and non-musicians.<sup>2</sup> In this clinical report we explore these distinctions in a patient with Alzheimer disease (AD).

**Case report.** A right-handed professional pianist with a family history of AD was evaluated for possible dementia. At age 58, she began to develop memory impairment, disorientation, and difficulties in visuospatial and executive functions. A year later she presented with psychotic depression and delusional paranoid

ideation. When seen at our clinic, both her Mini-Mental State Examination (MMSE) score of 22/30 and her Syndrome Kurztest (SKT) score of 12/27 were mildly to moderately impaired. Her scores were severely impaired on Part B of the Trail Making Test, on the Clock Drawing Test, and on a measure of Activities of Daily Living. A head CT scan and metabolic studies suggested a diagnosis of probable AD, and donepezil was prescribed.

When she was reassessed at age 63 she scored 10/30 on the MMSE, yet was able to read and interpret new, unfamiliar musical pieces. A single blind exploration was conducted over 7 days to compare her capacities to learn and to memorize verbal and musical material, both of which were presented in two modalities: visual and auditory.

Four learning tasks (two musical and two verbal) were administered each day. Recall was tested immediately, and at 1-minute and 10-minute intervals. Before and after the study period, she was evaluated with a battery of cognitive and behavioral tests. An MRI showed a diffuse mild cerebral atrophy and scattered foci of altered signal intensity in deep and periventricular white matter. The ECD SPECT scan revealed asymmetric hypoperfusion, predominantly in the left frontotemporal and parietal regions.

Over the course of the study, the patient was unable to recall verbal material, written or auditory. Also, she was unable to recall

## Musical Examples

a) Original as played on tape:

d) Day 4: One Minute Recall

e) Day 7: Immediate Recall

Figure. Musical material learned over a 7-day period: original, 1 minute recall (day 4), immediate recall (day 7).

the musical material presented in written form. However, she gradually learned the auditory musical material, which she began to recall on day 4. Although she chose the C major key instead of the original F, she had a good memory for the eight musical measures (figure) by day 7. Gradual improvements in overall performance and in rhythm, field elements, harmony, melodic accuracy, and sophistication in the accompaniment of the left hand were observed. No changes were detected in other cognitive functions over the period of the study. However, scores on the Geriatric Depression Scale decreased from 6 to 1 out of 15. Also, scores on the Neuropsychiatric Inventory improved, particularly the Agitation/Aggression scale score, which decreased from 18 to 12 out of 27. At follow-up a year later, she still enjoyed playing familiar musical tunes, despite further cognitive deterioration as evi-

denced by motor apraxia, aphasic errors, increased disorientation, and a MMSE score of 5.

**Discussion.** The persistence of creativity in cognitively impaired patients with AD is an evolving field of study.<sup>3,4</sup> In the case of preserved art painting, a possible explanation is that the most posterior visuospatial functions are relatively intact compared to more anterior and middle-temporal parietal impairment. With respect to music, a long-term memory subsystem specific to musical material has been detected in patients with bitemporal lesions.<sup>5</sup> Preservation of episodic memory for music may be subserved by the same brain neural networks as in non-Alzheimer's musicians.<sup>6</sup> Preserved motor skill learning and relatively intact perihippocampal cortical systems controlling basic language, praxis, attention, and visuospatial function may contribute. Similar to the violinist with moderate AD who learned and recalled new musical material,<sup>7</sup> our patient recalled a new composition. These studies demonstrate that retention of musical skills may be due to both preserved procedural and episodic memory. Further studies using activation MRI techniques could help us validate findings in this case study.

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## A second family with familial AD and the V717L APP mutation has a later age at onset

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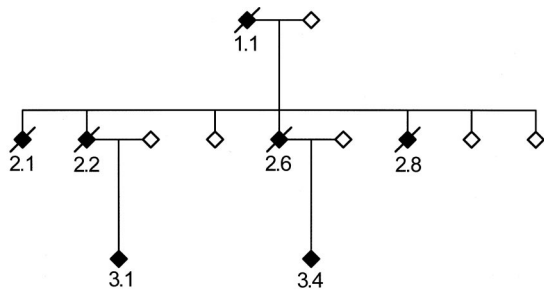
Four mutations have been reported at the 717 codon of the amyloid precursor protein (APP), with valine substituted by isoleucine, glycine, phenylalanine, and leucine. While several families with the isoleucine substitution have been described, the other substitutions have been reported in only one family each worldwide.

A family with the V717L APP mutation has been previously reported,<sup>1</sup> with a mean age at onset of 38 years (range 35 to 39), based on four affected family members, and a mean age at death of 46 years (range 40 to 50). We have identified a second family with a later mean age at onset of 50 years (range 48 to 57) and mean age at death of 61 years (range 57 to 68).

**Patients.** Family 171 is white and originates from England. We assessed Patients 3.1 and 3.4 and gathered information on other affected family members from medical records and the family (figure). Presymptomatic data are reported for Patient 3.4. Genetic analysis was performed as previously described.<sup>2</sup>

Patient 3.1 presented at age 50 years with a 2-year history of gradually progressive memory difficulties, with limited insight. The patient had imaginary conversations with a deceased relative. Neurologic examination revealed a pout and grasp reflex. Mini-Mental State Examination (MMSE) score was 25/30. Neuropsychology demonstrated intellectual decline with impaired memory and frontal function, but preserved visuospatial skills and naming. Brain CT showed generalized cerebral atrophy. EEG was normal, with preserved alpha rhythm. A year later cognition showed global decline. Genetic testing revealed the presence of the APP V717L mutation and ApoE ε3ε3.

Patient 3.4 (a woman) was enrolled in a study of individuals at risk for familial AD at age 49 years when she was asymptomatic. A clinical diagnosis of AD was made at age 54 years, after her family became concerned about her memory. On study entry, she was a teacher and described her memory as above average. Abnormalities on neuropsychological assessment were mild underperformance on measures of intelligence, impaired verbal recall and visual recognition memory, and frontal executive dysfunction. At age 51 years she reported no symptoms, although on testing memory was globally impaired and frontal dysfunction was again noted. However, IQ scores remained average and other cognitive domains were intact.



Individual	Age at onset - years	Age at death - years	Other features
1.1	48	58	None known
2.1	unknown	58	None known
2.2	48	57	None known
2.6	48	66	None known
2.8	57	68	Seizures
3.1	48	-	Hallucinations
3.4	51	-	Hallucinations
<b>Mean</b>	<b>50</b>	<b>61</b>	

Figure. (Top) Pedigree. (Bottom) Ages of affected members. — Indicates not known to have died.

She denied cognitive problems throughout. Family report was of subtle memory problems beginning around age 51 years, and definite symptoms since age 53 years. Genetic testing revealed the presence of the APP V717L mutation and ApoE  $\epsilon 3\epsilon 3$ . By age 55 years there was marked generalized cognitive impairment, with relative sparing of perception. Dyspraxia appeared following diagnosis but myoclonus was not a feature. She lived alone until age 57 years, and often appeared in conversation with an imaginary person. Later behavioral features included agitation and severe hyperorality, such that food had to be locked away. Brain MRI scans 5 and 3 years before diagnosis were both normal on visual inspection. However the registered<sup>3</sup> serial scans revealed progressive ventricular enlargement and hippocampal atrophy.

**Discussion.** Onset in this family was on average over a decade later than in the family previously reported,<sup>1</sup> although disease duration was similar in the two families, at around 10 years. All members of the previously reported family were homozygous for the ApoE  $\epsilon 3$  allele, as were both affected individuals in our family, so factors other than ApoE status must be causing the later age at onset. Our family has a more typical age at onset for APP mutations, the previous family having unusually early onset. The presence of imaging and neuropsychological evidence of disease 5 years before diagnosis in one individual suggests that the pathologic process may be in progress for substantially longer.

This family presented with progressive memory impairment typical of AD. The lack of insight was striking in Patient 3.4, who at no point admitted to symptoms, and also occurred to a lesser extent in Patient 3.1. Later atypical features were apparent, with hallucinations occurring in both patients, but not in the family previously reported with this mutation, nor with other APP mutations. Other features suggestive of cortical Lewy bodies were absent. There were no extrapyramidal features and perception was relatively spared. Lewy bodies can occur with the V717I APP mutation,<sup>4</sup> but pathologic examination has not yet been possible with this mutation.

Preimplantation diagnosis has been performed for this mutation<sup>5</sup> with resultant ethical debate.<sup>6</sup> Awareness of the later age at onset in some cases with this mutation will be important in advising family members about this and other genetic issues.

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**Isolated global amnesia associated with autoimmune thyroid disease**

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