Details of patients with myotonic dystrophy and hypersomnolence

Case	Age at evaluation	Age at diagnosis	Presenting symptom	MD severity	Intelligence	Age of EDS onset	PSG RDI	MSLT		HLA
								MSL	SOREM	
1	51	33	Weakness	Moderate	Normal	30s	2	2.3	2	DR11, 7 DRW52/53 DRW2/W3 DR5,6 DRW52 DQW1 DR6,7 DRW52/53 DQW1/W2
2*	34	18	Congenital	Severe	MR	Childhood	2	5.3	2	
3*	32	17	Congenital	Severe	MR	Childhood	54 (OSA)	7.3	None	
4	48	44	Weakness	Moderate	Normal	30's	82 (CSA) 10 (CSA)†	0.6	3	
5**	48	42	FH	Minimal	Normal	44	4	6.1	None	
6**	32	30	FH	Mild	Normal	<30	4			
7	33	17	FH	Moderate	Normal	20's	3.5			

EDS = excessive daytime sleepiness; FH = family history; HLA = human leucocyte antigen; MD = myotonic dystrophy; MR = mental retardation; MSL = mean sleep latency; MSLT = multiple sleep latency test; PSG = polysomnogram; RDI = respiratory disturbance index, calculated as the number of apnoeas and hypopnoea per hour of sleep; SOREM = sleep onset REM, defined as the onset of REM (at least one epoch) within 15 minutes of sleep onset; OSA = obstructive sleep apnoea; CSA = central sleep apnoea; *,**sibs; †second PSG and CPAP.

develop mild distal weakness (see table for additional clinical information). Each patient underwent at least one overnight polysomnogram in the Duke sleep disorders laboratory. A multiple sleep latency test (MSLT) was performed in five patients on the day after PSG. Four nap trials were performed at two hour intervals. Polysomnograms and MSLT were scored for sleep stages and sleep latency with standard criteria.²

All five patients had at least moderate hypersomnolence documented to confirm their presenting complaints. Three patients had at least two sleep onset REMs noted on the four nap trial. One patient (case 4) had accompanying sleep apnoea as a possible explanation for the MSLT findings. The other two patients had normal polysomnograms, however, and no other identified cause for the sleep onset REMs. No patients reported any auxiliary symptoms of narcolepsy. Three patients underwent human leucocyte antigen (HLA) typing; all were negative for DR2 but DQW1 was present in two patients (cases 2 and 3), who are black siblings.

Polysomnograms in myotonic dystrophy have shown various degrees of sleep disturbances and sleep related respiratory problems. Our review of the medical literature identified 86 patients including seven from this current study that have been reported with myotonic dystrophy and hypersomnolence. Ten per cent of the reported patients with hypersomnolence had documented alveolar hypoventilation. It has been suggested that the myotonic phenomenon itself or a concomitant hypoexcitability of the respiratory centre facilitate the onset of alveolar hypoventilation. This is often exacerbated by sleep, particularly REM sleep. Correction of the alveolar hypoventilation, however, has not led to an elimination of the hypersomnolence.³ Forty five cases (57%) of the reported patients with myotonic dystrophy and hypersomnia had some degree of sleep apnoea identified.^{3,4} The sleep apnoea was characterised as both central as well as obstructive. Respiratory disturbance index (RDI) ranges from mild to severe (RDI = 16–139). It is clear, however, that hypersomnolence often occurs in the absence of any identified sleep apnoea. No responses to treatment (including continuous positive airways pressure (CPAP)) were reported in these patients. As noted, one patient (case 4) in this series who had

primarily central sleep apnoea had significant reduction in his RDI from 82 to 10 after treatment with nasal CPAP. Surprisingly, he reported no benefit in terms of its effect on his daytime alertness with the use of CPAP over a one month home trial. He discontinued it of his own accord due to the perceived lack of efficacy. Hypersomnolence in five of our patients did respond to CNS stimulants (methylphenidate, pemoline).

The hypothesis of a primary central disturbance^{3,5} as a cause for hypersomnolence in myotonic dystrophy is supported by the presence of sleep onset REMs, which have previously been documented in one patient during both diurnal and nocturnal polysomnography.³ Manni *et al*⁶ in a recent report described 10 patients with myotonic dystrophy of whom five had subjective hypersomnia confirmed by MSLT but none had sleep onset REM. None of these patients reported any of the auxiliary symptoms of narcolepsy (cataplexy, sleep paralysis, and hypnagogic hallucinations) but all reported excessive daytime sleepiness. In our present series, three out of five patients studied with MSLT had two or more sleep onset REMs noted. The presence of sleep onset REMs in case 4 (RDI = 82) may be related to sleep disruption due to the associated sleep apnoea. Two cases (cases 1 and 2) had normal polysomnograms, hypersomnolence noted on MSLT (MSL = 2.3 and 5.3 minutes respectively), and two out of four sleep onset REM naps. Case 2 had a sleep onset REM on her nocturnal polysomnogram as well.

Of the three patients with sleep onset REMs noted, one patient (case 1) was negative for the usual HLA antigens (DR2 or DR2-DQW1) associated with narcolepsy. The HLA-DQW1 antigen was positive in the other two patients, who are black siblings. Of interest is that excessive daytime sleepiness was present before or at the time of diagnosis in six of the seven patients. Only in case 5, a man who was only diagnosed as having myotonic dystrophy because of an overwhelming family history (affected father, sister, children), did excessive daytime sleepiness develop after myotonic dystrophy was diagnosed. In this small series, overall severity of myotonic dystrophy disease or intelligence did not seem to be related to severity of excessive daytime sleepiness.

This report shows that the MSLT consis-

tently supported the subjective report of hypersomnolence, a common symptom in patients with myotonic dystrophy. Of particular note is the finding of pathological sleep onset REM in three of five patients studied, two of whom had no identified sleep disruption, sleep restriction, or drug treatment to explain this finding. None of the patients had any auxiliary symptoms of narcolepsy and the character of excessive daytime sleepiness was a persistent unrelenting sleepiness unaffected by naps. Therefore, there is little clinical information to suggest the diagnosis of narcolepsy. It is our judgement that these patients do not have a coincident occurrence of myotonic dystrophy and narcolepsy, but rather that myotonic dystrophy may have abnormal REM pressure as manifested by sleep onset REM naps on MSLT. This finding emphasises that other diseases besides narcolepsy can manifest shortened sleep latency and sleep onset REM on MSLT evaluation.

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Increase in adenosine metabolites in human cerebrospinal fluid after status epilepticus

Adenosine is a potent neuromodulator in the brain that may function as an endogenous anticonvulsant.¹ Adenosine analogues

are highly effective anticonvulsants against seizures induced in animals by a variety of mechanisms including kindling. Adenosine receptor antagonists exert proconvulsant actions indicating tonic adenosinergic control of ictal susceptibility. Animal studies have shown a rapid and substantial release of adenosine and its metabolites inosine and hypoxanthine in brain interstitial fluid during experimental seizures.² The physiological actions and metabolism of adenosine in the human CNS remain to be fully elucidated. We report that acute increases of adenosine metabolites can be detected in lumbar CSF after clinical status epilepticus in humans.

Seven patients with new onset status epilepticus were studied. Five patients (aged 12 to 67) developed generalised status epilepticus with three or more clonic or tonic-clonic seizures occurring in less than one hour without regaining consciousness between seizures. Causes included viral encephalitis, cysticercosis, uraemia, benzodiazepine withdrawal, and drug toxicity. One patient (48 years old) with diabetes and chronic renal failure developed epilepsy partialis continua involving repeated clonic seizures of the right face and arm. One patient (82 years old) experienced complex partial status epilepticus documented by electroencephalography due to withdrawal from alprazolam. Eleven patients (aged 22 to 53) evaluated for other neurological conditions (demyelinating neuropathy, headaches, cranial neuropathy, multiple sclerosis) were used as controls.

All CSF samples used in this study were discarded specimens from lumbar punctures performed for diagnostic purposes as part of each patient's clinical evaluation. The CSF was refrigerated at less than 4°C. Cell counts ranged from 0–30 white blood cells/mm³ and 0–92 red blood cells/mm³.

Nanomolar concentrations of adenosine were determined by high performance liquid chromatographic-fluorometric assay as described by Zhang *et al.*³ Micromolar concentrations of nucleosides and purine bases (for example, adenosine, inosine, and hypoxanthine) were determined by high performance liquid chromatographic assay using a Beckman Ultrasphere ODS 4-6 × 250 mm column eluted at 1.0 ml/min at ambient temperature with a gradient of buffer A (20 mM potassium phosphate pH 3.5) and buffer B (acetonitrile) (0–1 min, 0%; 1–18 min, 0–4%; 18–28 min, 4–7%; 28–33 min, 7–80% buffer B) and detection by ultraviolet absorbance at 254 nm.

Concentrations of adenosine in CSF obtained from control patients without seizures were in the low nanomolar range

whereas concentrations of the adenosine metabolites inosine and hypoxanthine were considerably higher (table). These values are comparable with those reported by other investigators.⁴ The concentrations of adenosine and its metabolites in lumbar CSF most likely reflect brain interstitial concentrations as the relative concentrations of these purine compounds in control samples are almost identical with those measured in the interstitial fluid from the frontal cortex of animals.² The low concentrations of adenosine cannot be attributed to ex vivo degradation as there is no appreciable metabolism of adenosine in CSF.⁴

Five patients evaluated for generalised convulsive status epilepticus underwent diagnostic lumbar punctures 0.1 to 13 hours after termination of their last seizure. No changes in CSF adenosine concentrations were found but inosine and hypoxanthine concentrations were substantially higher than controls (table). The time interval from the last seizure to CSF sampling seemed to be an important factor with the maximum increase of hypoxanthine (greater than sixfold) seen at one hour. Nevertheless, increases in inosine and hypoxanthine concentrations were still evident up to 13 hours. Patient 4 had another diagnostic lumbar puncture 12 days after recovery from her last seizure and all adenosine metabolites had returned to concentrations comparable with controls (adenosine < 0.039 µM, inosine 0.65 µM, hypoxanthine 2.31 µM). A sample of CSF from patient 6 with recurrent simple partial seizures showed a doubling in adenosine compared with the mean control value with a minimal increase in hypoxanthine. Patient 7 underwent lumbar puncture during continuous complex partial status epilepticus and a modest increase in adenosine and inosine but not hypoxanthine was found.

This study is the first to document rapid and substantial changes in adenosine metabolites in CSF after status epilepticus in humans. Our data complement the recent findings of During and Spencer⁵ who reported profound increases in extracellular fluid adenosine from the hippocampus in four patients with complex partial seizures, using microdialysis probes attached to depth electrodes. Our findings also closely parallel the reported changes in adenosine metabolites in interstitial fluid after experimental seizures in animals. For example, Park *et al.*² found that extracellular adenosine concentrations rose significantly during 10 minutes of bicuculline induced seizures in paralysed, ventilated piglets. Smaller increases in inosine and hypoxanthine were found during the same period. Ten minutes

after cessation of seizures, adenosine concentration returned to preictal values whereas inosine and hypoxanthine continued to rise, indicating that adenosine released interstitially during seizures is rapidly metabolised. Our findings of similar increases in inosine and hypoxanthine concentrations but not adenosine in patients after generalised status epilepticus can be explained by such rapid metabolism of adenosine in vivo.

The physiological relevance of our findings to the regulation of epileptic phenomena in humans is unknown. Extensive experimental data in animals indicate that adenosine and its metabolites are important endogenous modulators of seizure initiation and propagation.¹ Whether similar mechanisms are operative in humans remains to be determined.

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Bilateral cavernous sinus thrombosis causing Korsakoff's amnesic syndrome

Korsakoff's amnesic syndrome (Korsakoff's psychosis) is a condition in which learning and memory are affected out of proportion to other cognitive functions. It has not been previously reported as a complication of cavernous sinus thrombosis. Our patient developed Korsakoff's amnesic syndrome after bilateral medial temporo-occipital infarcts as a complication of cavernous sinus thrombosis.

A 44 year old man was admitted with fever of 15 days duration, and altered sensorium of 10 days duration preceded by a day of recurrent vomiting. Three days before admission he developed painful swelling of his left eye associated with redness and sudden total loss of vision in that eye. The fever was high grade, intermittent, and associated with sweating. The altered sensorium was in the form of restlessness, incoherent speech, disorientation, and an inability to recognise his relatives properly. He had had hypertension for four years duration, was on irregular treatment, and was a past smoker. He had no history of alcohol intake.

On examination he was drowsy, febrile (99°F), and had a blood pressure of

Cerebrospinal fluid concentrations of adenosine and metabolites after status epilepticus

Seizure	Time(h)	Adenosine (µM)	Inosine (µM)	Hypoxanthine (µM)
Controls (n = 11) (mean (range))	—	0.063 (0.039–0.106)	0.41 (ND–0.79)	2.36 (1.27–4.08)
Patients:				
1 GTC	<1.0	0.050	1.47	12.42
2 GTC	1.0	0.040	1.91	15.78
3 GTC	4.0	0.061	ND	15.39
4 GTC	9.0	0.072	2.47	8.20
5 GTC	13.0	0.027	0.71	4.34
6 EPC	—	0.120	ND	3.20
7 CPSE	—	0.102	1.33	1.98

ND = none detected; GTC = generalised tonic-clonic status epilepticus; EPC = epilepsy partialis continua; CPSE = complex partial status epilepticus; time = estimated time from last seizure to sampling of CSF. Patient 7 was sampled during continuous seizure activity. Patient 6 had multiple simple partial motor seizures and time from last seizure is not available.