CSF HYPOCRETIN CONCENTRATION IN VARIOUS NEUROLOGICAL AND SLEEP DISORDERS

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(received 3 February 2011, accepted 14 February 2011)

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Abstract

Recent CSF and postmortem brain hypocretin measurements in human narcolepsy suggest that hypocretin deficiency is involved in the pathophysiology of the disease. Thus, it is important to study whether neurological disorders also have abnormal CSF hypocretin levels. We therefore measured hypocretins in the CSF of various neurological disorders and obstructive sleep apnea syndrome (OSAS) to identify altered hypocretin levels. CSF hypocretin levels in patients with OSAS and neurological diseases were almost within the normal range in Japanese populations. While, hypocretin levels in patients with narcolepsy-cataplexy are very low. The measurement of hypocretin levels is a useful diagnostic tool in Japanese patients with narcolepsy-cataplexy.

Key word : Hypocretin, Narcolepsy, OSAS

Introduction

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy and other abnormal manifestations of REM sleep, such as sleep paralysis and hypnagogic hallucinations (i.e. narcolepsy tetrad) as well as disturbed nighttime sleep (i.e. narcolepsy pentad). This sleep disorder affecting 1/600 Japanese, is associated with HLA-DR2 (DQB1*0602)[1-3)]. Recent CSF and postmortem brain hypocretin measurements in human narcolepsy suggest that hypocretin deficiency is involved in the pathophysiology of the disease[1,2)]. Thus, it is important to study whether neurological disorders also have abnormal CSF hypocretin levels[3)]. We therefore measured hypocretins in the CSF of various neurological disorders and obstructive sleep apnea syndrome (OSAS) to identify altered hypocretin levels. The results will also be useful in further evaluating the specificity of low hypocretin levels in narcolepsy-cataplexy among Japanese populations.

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Methods

There were a total of 218 patients with narcolepsy-cataplexy, obstructive sleep apnea and neurological disorders. CSF was collected from patients with narcolepsy-cataplexy (n=12)[4)], obstructive sleep apnea syndrome (OSAS, n=16)[5)], neurodegenerative disorders, such as (Alzheimer's disease and Alzheimer type dementia (AD, n=9) and Parkinson's disease (PD, n=19), intracranial neoplasms (n=5), multiple sclerosis (n=10), infections (i.e. meningitis and encephalitis) (n=23), inflammatory neuropathy, such as Guillian-Barre syndrome (GBS) (n=16)[6)], poliomyelitis (n=35), epileptic seizures (n=22)[7)], motor neuron diseases (n=8), hematological disorders (ALL and AML n=11, malignant lymphoma n=5)[7)], congenital abnormalities (n=12)[7)] and cerebro-

vascular disorders (CVD, $n=20$). Either patients or families gave informed consent for the lumbar puncture. Several results of various disorders were previously reported[4-7]. CSF hypocretin-1 was measured in crude CSF samples (0.1 ml duplicate) using a commercially available radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals). Intra-assay variability was 4.3% and the detection limit was 40 pg/ml. The study was approved by the ethics committee of Akita University. For statistical analysis, the Bonferroni/Dun test was used. The significant level was set at $P<0.0167$.

Results

Hypocretin levels were very low in the majority of patients with narcolepsy-cataplexy (mean+/−SD, 98+/−91 pg/ml, 10 out of 12 cases are lower than 110 pg/ml, Table 1). These levels were significantly different from other neurological diseases ($P=0.001$). Hypocretin levels in patients with OSAS (289+/−90 pg/ml) and neurodegenerative disorders (AD: 282+/−63 pg/ml, PD 289+/−66 pg/ml) were within the control range (>200 pg/ml). Levels in patients with multiple sclerosis (273+/−54 pg/ml), infections (i.e. meningitis and encephalitis, 273+/−62 pg/ml) or poliomyelitis (292+/−27 pg/ml), epileptic seizures (305+/−55 pg/ml), motor neuron diseases (308+/−31 pg/ml), hematological disorders (304+/−44 pg/ml), congenital abnormalities (289+/−87 pg/ml) and cerebrovascular disorders (320+/−99 pg/ml) were in the control range. However, two OSAS, one AD, three PD, two infection, one epileptic seizure, two congenital abnormalities and two CVD patients were lower than 200 pg/ml. Patients with intracranial neoplasms were also in the control range (232+/−20 pg/ml), except for a patient with hypothalamic tumor (102 pg/ml). GBS patients had slightly lower hypocretin levels (206+/−72 pg/ml). CSF hypocretin levels in 5 out of 16 of these patients were lower than 200 pg/ml (64, 103, 123, 155, 181 pg/ml).

Discussions

Recent CSF hypocretin measurements and post-mortem studies in narcolepsy suggest that hypocretin deficiency is the major pathophysiology of the disease[1,2]. CSF hypocretin in various neurological and sleep disorders further demonstrated that a low hypocretin level is highly specific to narcolepsy-cataplexy[3] and this measurement is now being established as a new diagnostic tool[8,9]. Mignot *et al*. proposed that hypocretin

Table 1. CSF Hypocretin Concentrations in Various Diseases

diseases	*n*	mean+/−SD	<110 pg/ml	110-200 pg/ml	>200 pg/ml
narcolepsy-cataplexy	12	98+/−91	*n*=10	*n*=2	0
OSAS	16	284+/−74	−	1	15
AD	9	282+/−63	−	1	8
PD	19	289+/−66	−	3	16
intracranial neoplasms	5	232+/−20	1	−	4
multiple sclerosis	10	273+/−54	−	−	10
infections	23	273+/−62	−	2	21
GBS	16	206+/−72	2	3	11
poliomyelitis	35	292+/−27	−	−	35
epileptic seizures	22	305+/−55	−	1	21
motor neuron diseases	8	308+/−31	−	−	8
hematological disorders	11	304+/−44	−	−	11
congenital abnormalities	12	289+/−87	−	2	10
CVD	20	320+/−99	−	2	18
total number	218		13	17	188

levels below 110 pg/mL were diagnostic for narcolepsy and values above 200 pg/mL were considered normal[9].

The majority of narcoleptic subjects in this study had extremely low hypocretin levels (<110 pg/ml)[4]. Although a significant decrease in CSF hypocretin levels was observed in some GBS patients[6], levels in patients with OSAS[5] and neurological diseases such as AD, PD, MS, CNS infections and other disorders were almost within the normal range (>200 pg/ml, 188/206 cases) in Japanese populations. CSF hypocretin levels in patients with AD and PD, two conditions with established sleep abnormalities[10,11], were normal. Dysfunction of other neurochemical systems, for example dopaminergic and cholinergic systems in PD and AD, may be more directly involved in sleep abnormalities in these subjects[10,11]. OSAS is a disabling condition characterized by secondary excessive daytime sleepiness, severe snoring, repeated episodes of upper airway obstruction during sleep, and nocturnal hypoxemia[5]. Among sleep disorders, idiopathic hypersomnia[4] and OSAS, hypocretin levels were normal[5], suggesting that low hypocretin levels are highly specific for narcolepsy-cataplexy.

The biological markers of diagnosing for narcolepsy-cataplexy, such as nocturnal polysomnography (PSG), multiple sleep latency test (MSLT) and HLA-DR2 (DQB1*0602) test, are not easy to perform for most general hospitals. In addition, the HLA test is not sufficient for positive diagnosis of narcolepsy. The measurement of hypocretin level is a useful diagnostic tool in Japanese patients with narcolepsy-cataplexy, especially when other diagnostic measures (e.g. nocturnal PSG, MSLT and HLA) are not sufficient.

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