Sleep Disturbances and Hypocretin Deficiency in Niemann-Pick Disease Type C

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Design and Patients: Subjects with Niemann-Pick disease, type C have been reported to display narcolepsylike symptoms, including cataplexy. In this study, 5 patients with juvenile Niemann-Pick disease were evaluted for sleep abnormalities using nocturnal polysomnography, clinical evaluation, and the Multiple Sleep Latency Test. HLA typing and cerebrospinal fluid hypocretin levels were also evaluated in 4 patients. Niemann-Pick disease diagnosis was confirmed in all cases biochemically and by the presence of foam cells in the bone marrow.

Results: Deterioration of intellectual function; the presence of pyramidal, dystonic and cerebellar features; and splenomegaly were observed in all cases. Cataplexy was reported in 1 patient. Nocturnal polysomnography revealed disrupted sleep in all patients. Total sleep time, sleep efficiency, rapid eye movement sleep, and delta sleep amounts were decreased when compared to age-matched controls. Altered sleep patterns included sudden increases in muscle tone during delta sleep, electroencephalographic sigma activity connected with rapid eye movements and muscle atonia, atypical K-complexes and spindle activity, and the presence of alpha-delta sleep. All Niemann-Pick disease cases exhibited fragmentary myoclonus. Shortened mean sleep latencies were observed in 3 patients during the Multiple Sleep Latency Test, but sleep-onset rapid eye movement periods were observed only in the case with cataplexy. This patient was HLA DQB1*0602 positive, while the other subjects were HLA negative. Cerebrospinal fluid hypocretin-1 levels were reduced in 2 patients (1 with cataplexy) while in the 2 other patients, the levels were at the lower range of the normal values. Hypocretin levels in the Niemann-Pick disease group (204.8±39.3pg/mL) were significantly reduced when compared to controls (265.8±48.8 pg/mL).

Conclusions: The findings suggest that lysozomal storage abnormalities in Niemann-Pick disease patients may impact the hypothalamus and, more specifically, hypocretin-containing cells. These changes might be partially responsible for sleep abnormalities and cataplexy in patients with Niemann-Pick disease.

Key Words: Niemann-Pick disease – type C, sleep architecture, changes of microstructure, fragmentary myoclonus, cataplexy, diminished hypocretin-1 level, cerebrospinal fluid

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INTRODUCTION

NIEMANN-PICK C DISEASE (NPC) IS A FATAL, AUTOSOMAL RECESSIVE DISORDER WITH AN ESTIMATED PREVALENCE OF 1:150.000 IN WESTERN EUROPE. Biochemically, it is characterized by extensive lysosomal accumulation of unesterified cholesterol in many tissues, as well as lysosomal storage of sphingolipids in some tissues such as liver and brain.[1-4] The clinical manifestation and severity of individual NPC cases are extremely variable. Classic symptoms include hepatosplenomegaly, vertical supranuclear gaze palsy, ataxia, dystonia, and dementia. Interestingly, several cases of NPC with cataplexy have been reported.[5-8] In cataplexy, sudden and brief episodes of bilateral loss of muscle tone are observed during strong emotions such as laughing or anger.[9]

Most individuals with NPC have mutations in the Niemann-Pick C1 gene (NPC1).[10,11] More rarely, subjects with NPC have mutations in another gene, NPC2.[12] Although the function of the NPC1 protein is not fully understood, it is believed to regulate the intracellular transport of low–density-lipoprotein-derived free cholesterol.[13] Little is known regarding the normal function of NPC2, but cholesterol transport abormalities are also observed.

Disclosure Statement

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The association of cataplexy and NPC is fairly unique.[8] Wheras sleepiness and other narcolepsy symptoms are observed in many other conditions, cataplexy is almost pathognomonic for the sleep disorder narcolepsy. In NPC cases with cataplexy, triggers for muscle-atonia episodes are typical, and the symptom responds to antidepressant therapy, as does the cataplexy of the narcolepsy syndrome. Recent studies have shown reduced hypocretin-1 (Hcrt-1) levels in the cerebrospinal fluid (CSF) of narcoleptic patients with cataplexy.[14-17] In contrast, most narcolepsy or hypersomnia cases without cataplexy have normal CSF Hcrt-1 levels.[16,17] Hypocretin peptides are only synthesized in neurons of the perifornical, lateral, and posterior hypothalamus,[18] but the anatomic projection of the Hcrt neurons is widespread to the most brain structures, including those important for the regulation of vigilance and locomotor activity.[19,20] In human narcolepsy, an apparent loss of Hcrt-containing neurons has been reported in postmortem studies.[21,22] Together with the fact that narcolepsy is tighly HLA associated,[23,24] the finding suggests a possible autoimune basis for most cases of human narcolepsy.

In the current study, 5 patients suffering from NPC were evaluated for potential sleep abnormalities using nocturnal polysomnography (PSG) and the Multiple Sleep Latency Test (MSLT). HLA typing was performed, and CSF Hcrt-1 levels were analyzed in 4 patients.

METHODS

Subjects

Five patients with NPC (3 female, 2 male, mean age 23.0 ± 6.2 years, 3 with familial predisposition) were included. Foam cells were identified in the bone-marrow aspirate with the storage pattern corresponding to NPC.[1] The diagnosis was confirmed by providing deficient cholesterol esterification (done by Dr. M.T.Vanier, Lyon, France).

Twelve healthy subjects (5 female, 7 male, mean age 21.6 ± 5.0 years) were included as controls for the PSG studies. These subjects did not use

psychotropic compounds, had no complaints suggesting a sleep disorder, and reported standard sleep/wake habits. Ten additional age- (25.2 ± 3.3 years) and gender-matched (6 female and 4 male) healthy subjects were used as controls for CSF Hcrt-1 analyses. All control and NPC subjects gave informed consent.

Polysomnographic Recordings

Psychotropic medications (diazepam in 1 case) were discontinued 5 days before PSG investigations. Subjects spent at least 1 night hospitalized on the ward under standard condition before experimental nocturmal PSG was performed. A Schwarzer polygraph was used for all sleep recordings. All PSG studies were performed using a standard electroencephalographic (EEG) montage (F4-C4, C4-F8, C4-P4, F3-P3, C3-F7, C3-P3, C3-A2), submental electromyography (EMG) and horizontal electrooculography (EOG). Electrocardiogram, bilateral anterior tibialis EMG, and a videorecording using an infrared camera were also studied. Airflow was monitored at the nose and mouth using thermistors. The MSLT was conducted the day following nocturnal PSG. Naps were recorded at 0900, 1100, 1300, 1500, and 1700 hours. The EEG (C4-A1, C3-A2), horizontal and vertical EOG, and submental EMG were employed for the daytime nap tests.[25] A sleep-onset rapid eye movement (REM) period (SOREMP) was defined in terms of REM periods within 10 minutes of sleep onset. In all cases, sleep stages were visually scored according to the standard criteria.[26]

HLA Oligotyping and Hcrt Radioimmunoassay

The HLA DQB1 * 0602 testing was performed as previously described.[23] Immunoreactive Hcrt-1 was measured in the CSF of 4 NPC patients and 10 age- and gender-matched controls. The CSF samples were immediately frozen, coded, and shipped to Stanford University; Hcrt-1 was extracted from 1 millileter of CSF (second fraction of 1.5 mL) with a reversed phase SEP-PAK C18 column.[14] Iodine[125] Hcrt-1 radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA, USA) was used to measure levels in reconstituted aliquots (duplicate analysis was done on all of the samples).

Table 1—Clinical features, sleep parameters, and cerebrospinal fluid hypocretin-1 levels of patients with Niemann-Pick disease type C

Parameter	NPC patients				
	1	2	3	4	5
Sex/Age (yrs)	F/14	F/25	M/24	F/21	M/31
PSG parameters					
Total sleep time (h:min)	6:56	5:28	2:56	3:19	2:45
Sleep efficiency (%)	79	71	35	57	31
Sleep latencies (min)					
Sleep onset	4	13	12	2	2
REM	146	165	306	110	46
SWS	9	12	11	8	10
Sleep stages (%TST)					
NREM 1	2.8	5.2	3	6.9	7.6
NREM 2	33	43.4	10	19.8	61.9
NREM 3	2.9	1.7	2.4	4.6	9.8
NREM 4	18.4	13.7	24.2	17.2	9.8
REM	23	9.1	5.5	10.1	0.6
Wake	19.1	26.9	54.7	39.1	10.4
Fragmental myoclonus	+	+	+	+	+
AHI	-	2	1	3	2
PLMI	-	1	-	-	-
MSLT parameters					
Mean sleep latency (min)	5.1	3.5	3.2	10.4	10.7
SOREMPs (#)	1	0	0	0	0
CSF Hcrt-1 levels					
Crude	176	297.3	347.9	Not tested	143
Extract	157	226.3	245.7	Not tested	190

PSG, polysomnography; REM, rapid eye movement; SWS, slow wave sleep; TST, total sleep time; NREM, non-rapid eye movement; AHI, apnea-hypopnea index; PLMI, periodic limb movement index; MSLT, Multiple Sleep Latency Test; SOREMP, sleep-onset rapid eye movement periods; CSF, cerebrospinal fluid; hcrt-1, hypocretin-1

Statistics

Statgraphics was used for all statistical analysis. Comparisons between groups were performed using Mann-Whitney U tests or *t*-tests.

RESULTS

Clinical Evaluation of the NPC Cases

At the time of study, findings observed in all cases were mental retardation, quadrispasticity, dystonic/dyskinetic syndrome, and neo/paleocerebellar syndrome. Vertical gaze palsy was present in 3 cases. Cataplexy was observed in only 1 patient. Cataplectic attacks were mostly associated with weakness of face, neck, and leg muscles (rarely with fall to the floor), lasting about 30 seconds, without any alteration of consciousness, triggered by laughter, hearing and telling jokes, or when angry, typically with several epizodes per week and very poor response to therapy (imipramine 75mg, clomipramine 100mg, fluoxetine 20mg). None of our patients suffered from excessive daytime sleepiness or other sleep disorders, including parasomnias. Splenomegaly was found in all subjects (range 12-18 cm). Routine hematologic and biochemical profiles were unremarkable. Head computed tomography and magnetic resonance imaging revealed mild difuse cerebral atrophy, especially in periventricular areas and the cerebellum. Awake EEG evaluation showed mild slowing with nonspecific abnormalities in the posterior head regions. The visual and somatosensory evoked potentials in the *n.tibialis* and *n.medialis* were slighly or moderately abnormal; the brainstem auditory evoked potentials were delayed in 4 of our patients.

Neuropsychologic testing showed memory and concentration impairment and evidence of proportional sparing of concrete verbal skills. Testing revealed a Verbal IQ range of 64 to 72, a Performance IQ range of 55 to 66, and Full-Scale IQ range of 59 to 74 on the WISC-R test. The WISC-R was not applicable in 1 patient due to nomcompliace and strong tiredness. In this case, only Raven's test was used for testing (nonverbal skills).

Nocturnal PSG

At the quantitative level, significant differences were observed between NPC and age-matched controls. In all patients (n=5), sleep was fragmented and disorganized. Total sleep time was decreased ($p<0.01$), and sleep efficiency was lowered ($p < 0.001$). Patients were found to have a shorter sleep latency ($p < 0.01$) and exhibited increased time awake after sleep onset ($p < 0.05$). Decreased amounts of REM sleep ($p < 0.05$) and delta sleep ($p < 0.05$) were observed. Latency to delta sleep was reduced ($p < 0.05$). Interestingly, in the NPC subject suffering from cataplexy, percentage of REM sleep (23%) and REM latency (146 min) were not diminished, and sleep architecture was similar to that of NPC patients without cataplexy (Table 1).

Nocturnal PSG also differed qualitatively from control subjects, In all patients, sudden increases in muscle tone were observed during delta sleep, and EEG sigma activity was connected with REMs and muscle atonia (Figure 1). Except typical K-complexes and sleep spindles, we observed atypical forms of these graphoelements, which differed in amplitude or frequency from case to case (Figure 2). We also observed alpha superimposition on delta waves during non-REM sleep or alpha-delta alternations. In these cases, alpha waves had relatively high amplitudes and were 1 to 2 Hz slower than waking alpha activity. In all recordings, fragmentary myoclonus (FM) was present without any predilection to specific sleep stage. The FM was described as muscle potentials of 50 to 200 μV in amplitude and less than 150 milliseconds in duration, using surface EMG electrodes.[27]

Of note, nocturnal SOREMPs were never observed, and none of the patient exhibited significant sleep apnea syndrome or periodic leg movements during sleep.

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Multiple Sleep Latency Test

Mean sleep latencies were lower than corresponding control MSLT guideline values (Table 1) in both subjects with and without cataplexy (mean value 6.58±3.15 min). Interestingly, the NPC patient suffering from cataplexy exhibited a single SOREMP in the first daytime nap of the MSLT.

HLA Results and CSF Hcrt-1 Levels

The patient with cataplexy was HLA DQB1* 0602 positive, while all other subjects were HLA negative. All controls were HLA DQB1* 0602 negative. Extracted CSF Hcrt-1 levels were found to be moderately lower in NPC subjects when compared to the controls (Table 1). The Hcrt-1 levels were lowest in 2 patients, 1 with (157 pg/mL) and 1 without cataplexy (190 pg/mL). The levels in the remaining 2 patients were at the lower limit of normal levels. The mean value of Hcrt-1 (204.8±39.3pg/mL) in the NPC group was significantly lower than in the controls (265.8±48.8 pg/mL) ($p<0.05$).

DISCUSSION

Our study is the first to systematically evaluate nocturnal sleep, sleepiness, HLA typing, and Hcrt-1 levels in a case series of patients with NPC. Niemann-Pick C disease is unique as it is one of the few neurologic disorders where typical cataplexy can be reported.[5,7,28,29] In a systematic review of early-onset narcolepsy cases, Challamel et al[8] presented this association in 12 of 20 cases of patients with symptomatic narcolepy. Vanier[30] reported cataplectic attacts in more than 10% of NPC cases. Interestingly, an atypical form of NPC, clinically presenting as isolated cataplexy, was reported in a 4-year-old child.[6] In spite of this unusual association, however, sleep studies have never been performed in NPC cases.

We found that only 1 of 5 NPC subjects exhibited cataplexy. In contrast, all 5 NPC patients exhibited nocturnal-sleep and MSLT abnormalities. These included 1) abnormal nocturnal sleep macroarchitecture such as a decrease in total sleep time, sleep efficiency, REM, and delta sleep and a higher percentage of wake time after sleep onset; 2) abnormal sleep microstructure such as regressive forms of sigma activity and alpha-delta sleep (alpha rhythm appearing during delta sleep); 3) occurence of FM; and 4) in 3 of 5 patients, shortened MSLT mean sleep latencies and only in the NPC patient suffering from cataplexy, a single SOREMP on MSLT.

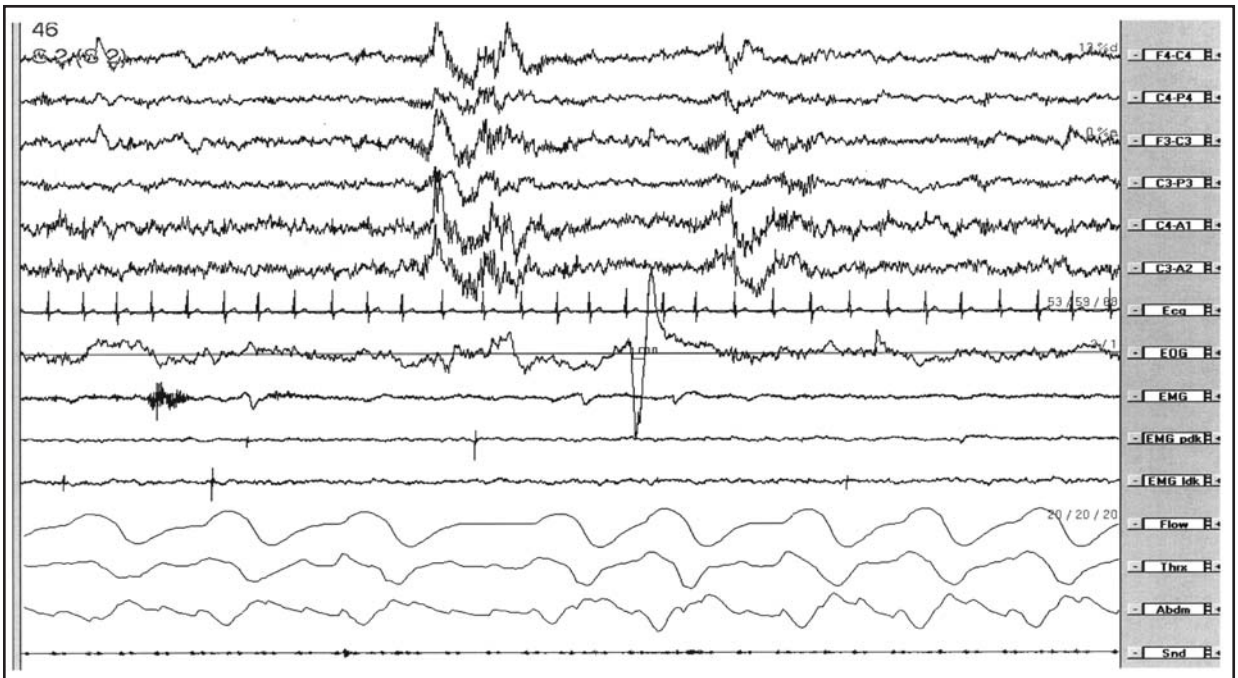

Figure 1—Sigma activity connected with rapid eye movements and muscle atonia in Niemann-Pick disease type C.

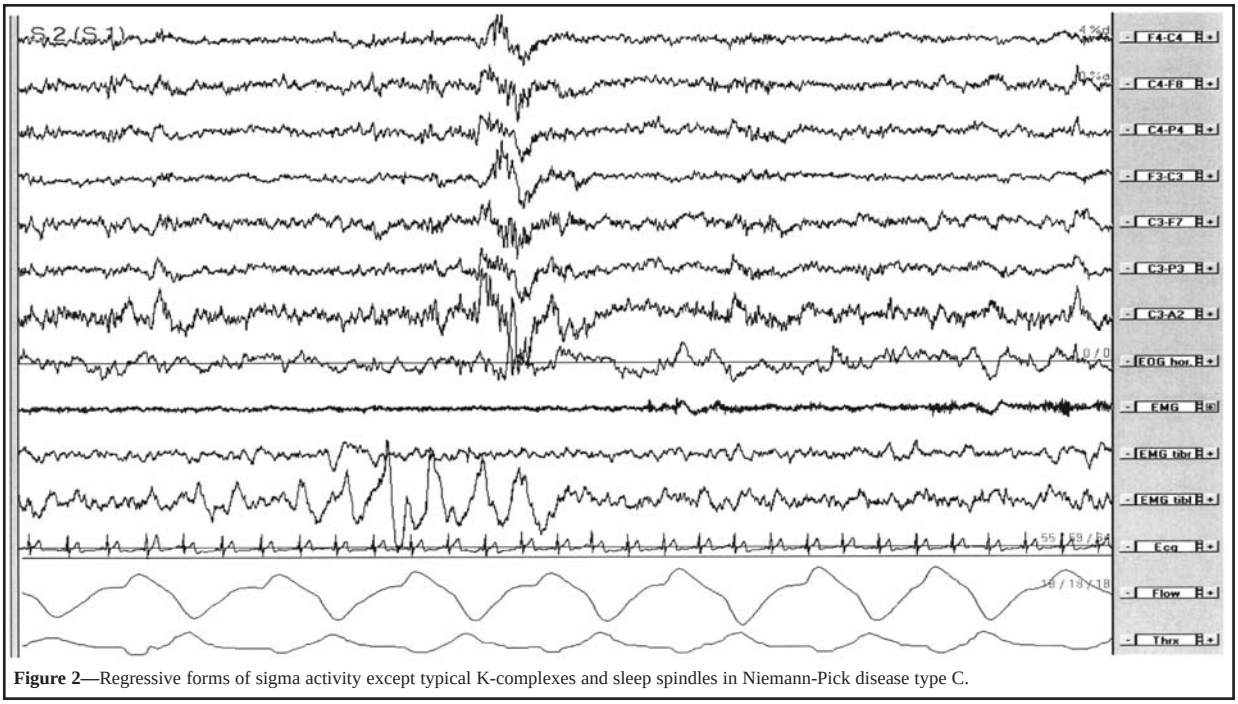

Figure 2—Regressive forms of sigma activity except typical K-complexes and sleep spindles in Niemann-Pick disease type C.

At the neurochemical and genetic level, Hcrt-1 levels were generally lower in the NPC group, but none of the values observed were in the narcolepsy range. In a recent systematic study including 274 patients with narcolepsy and hypersomnia and 296 controls (healthy

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and with neurologic disorders), Hcrt-1 values below110 pg/mL were considered diagnostic for narcolepsy while extracted CSF values above 150 pg/mL were considered in the normal range (<200 pg/mL in the direct assay).[17] In 2 NPC cases, extracted values were in the intermediate-low range (157 pg/mL and 190 pg/mL), and the subject with the lowest value exhibited cataplexy. Interestingly, this patient was the only HLA DQB1*0602 positive subject among 4 NPC subjects. The Hcrt-1 levels in 2 other subjects were also relatively low, contributing to the significantly lower mean CSF Hcrt-1 level in the NPC group compared to the controls (Table 1). These results, therefore, suggest moderately impaired Hcrt tranmission in NPC, with the caveat that intermediate-low values are also observed in numerous other neurologic conditions such as head trauma and encephalitis[31] and may be of uncertain functional significance.[31]

The importance of Hcrt transmission in the pathophysiology of narcolepsy-cataplexy has been suggested by the finding in animals models.[32,33] Subsequent human studies in the CSF and postmortem brain have revealed that a large majority of narcoleptic-cataplectic subjects are associated with loss of production of Hcrt ligands both in the CSF and brain, possibly due to the selective loss of Hcrt neurons in the lateral hypothalamic area.[14,21,22,34]

In NPC, the cardinal pathophysiologic feature is the existence of foamy storage cells in visceral organs and the accumulation of lipid-storage materials in neurons and glial cells of the nervous system. Cortical neurons, especially large pyramidal neurons in the deep cortical layers, larger neurons in the basal ganglia and thalamus, show distended cytoplasm. The degree and distribution of this cytoplasmic ballooning may vary considerably in individual cases.[35,36] Neuroaxonal dystrophy in the form of axonal spheroids is found throughout the neuraxis, in particular in the thalamus, dentate nucleus, and midbrain nuclei, including the substantia nigra.[4] The cerebellum is variably affected by this process–Purkinje and granular cells are lost and replaced by dense fibrillary gliosis[37] or Purkinje cells and Golgi cells show distended perikarya with storage material.[38] The finding that CSF Hcrt-1 levels are moderately reduced in 2 cases of NPC suggests that the lipid dysregulation might also affect Hcrt-containing cells in the lateral hypothalamus. The fact that all our NPC subjects exhibited sleep abnormalities, regardless of CSF Hcrt levels, however, suggests that pathology in other brain structures probably contributes to the sleep phenotype in NPC. It can also be argued that disturbed nocturnal sleep in all NPC cases contributes to daytime sleepiness in all cases.

The CSF Hcrt measurements in hypersomnia subjects have recently shown that Hcrt deficiency is highly correlated with the occurrence of cataplexy and HLA-DQB1*0602 positivity.[24] Consistent with the previous reports of a high incidence of cataplexy in NPC patients, 1 of our NPC patients also exhibited cataplexy. In a separate study on Japanese patients suffering from NPC, 1 patient with cataplexy also had low a CSF Hcrt-1 level, while other subjects showed normal levels [39]. Thus, impaired Hcrt neurotransmission in addition to the global brain dysfuction may be required for the occurrence of cataplexy. However, the finding of low CSF Hcrt may not be sufficient for clinical manifestation of cataplexy. A low Hcrt-1 level was found in one HLA DQB1*0602-negative case in our study, but no cataplexy was noticed in this subject. It may be hypothetized that HLA positivity, NPC mutations, and Hcrt-1 deficiency all contribute to the clinical picture with regard to the presence of a sleep phenotype.

We conclude that sleep abnormalities in NPC patients may result from a lysozomal storage defect in various brain structures, while cataplexy may be related to a more-specific, albeit partial, loss of Hcrt in the lateral hypothalamus. The mechanisms underlying cell death in NPC are not known. Similarly, how Hcrt deficiency can lead to the occurrence of cataplexy is not well understood. Further studies in humans and animal models will be needed to extend this finding.

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