INTRODUCTION

RECENT CSF AND POSTMORTEM BRAIN HYPOCRETIN MEASUREMENTS IN HUMAN NARCOLEPSY SUGGEST THAT HYPOCRETIN DEFICIENCY IS INVOLVED IN THE PATHOPHYSIOLOGY OF THE DISEASE.1,2 Extended studies in idiopathic and symptomatic narcolepsy, as well as in various neurological conditions, suggest that CSF hypocretin-1 measures could be used as a diagnostic tool for narcolepsy.3,4 Although the levels in selected healthy adult populations tested fall in a relatively narrow range (age: 22-62 years old, range: 230-376 pg/ml, mean+/-SD: 280+/-33 pg/ml),3 whether CSF hypocretin-1 levels fluctuate with age or by gender has not been fully studied. This information is essential for understanding the pathogenesis of hypocretin deficiency in narcoleptic subjects. In order to investigate the developmental change of hypocretin concentrations, we measured CSF hypocretin-1 levels across an age range from infants to elderly people.

METHODS

Since it is shown that CSF hypocretin-1 can be reliably measured in frozen CSF stored for several years,3 we used CSF samples collected for diagnostic purposes (storage period: one week to three years, -80C freezer). Two hundred seventy-two patients were included in this study, with 157 males and 115 females (0-79 years old). The ethnicity of all subjects was Japanese. The patients were diagnosed by clinical inspection, radiological and laboratory examinations. The diagnoses were malformations (n=19), metabolic diseases (n=10), hematological diseases (n=16), infections of the central nervous system (n=36), other neurological disorders (n=130), narcolepsy (n=5), Guillain Barre Syndrome (GBS, n=11), and others (n=46). Either patients or families gave informed consent for the lumbar puncture and for the biochemical analysis of the CSF. Hypocretin-1 was measured in CSF samples at Akita University using 125-I radioimmunoassay kits (Phoenix Pharmaceuticals, Belmont, CA) as previously reported by Nishino et al.1,3 The detection limit was 40 pg/ml. Comparisons of age groups and genders were made by using two-way ANOVA. Since CSF hypocretin-1 levels from patients with narcolepsy1,3 and GBS4 were reported to be significantly low, samples from these patients were excluded from the statistical analysis.

RESULTS

The CSF hypocretin-1 levels of age groups are shown in Figure 1. In our sample population, there was no significant difference in CSF hypocretin-1 levels between females and males (females: 291+/-65 pg/ml, males: 290+/-67 pg/ml, mean+/-SD), nor between any age groups. In the current study, samples from 15 infants (age<1) were included and seven of them were under four months. The mean hypocretin-1 levels of these seven infants were 264pg/ml, which is almost the same range of adult groups. On the other hand, the samples from all Japanese narcoleptic patients tested (n=5, age: 6, 7, 24, 27, 68 years old) were under the detection limit, suggesting that the hypocretin deficiency
occurs in narcolepsy regardless of ethnicity and age. Two cases of GBS showed low concentrations of 65pg/ml and 125pg/ml, below the mean minus 2 SD. However, no other disorders had a clear trend for low or high hypocretin-1 levels.

DISCUSSION

It was reported that expression of prepro-hypocretin mRNA in the rat hypothalamus was weakly detected at the perinatal period and increased gradually during neonatal and infantile periods. In the weaning period, mRNA expression markedly increased and then reached a plateau through the pubertal period to the adult period. On the other hand, immunohistochemistry in the rat brain demonstrated that hypocretin neurons already exist at the end of the embryonic period, although the cell size is smaller and is gradually enlarged after birth. In this current study, we measured seven CSF samples from the pre-weaning period (under four months old). CSF hypocretin-1 levels are consistently detected in these infants and the range is similar to that in adults, suggesting CSF hypocretin neuro-transmission was already established at birth. In addition, two narcoleptic patients were diagnosed at six- and seven years-old, indicated that the hypocretin deficiency can occur in pre-pubertal children.

Although our samples constitute a heterogeneous group with various kinds of disease conditions, hypocretin-1 levels are not different in respect to gender or age groups. Thus, the undetectable CSF hypocretin-1 levels seen in narcolepsy are highly abnormal regardless of age. This examination must be valuable for the decisive and early diagnosis of narcolepsy in all age groups. Further studies are needed to determine when a decrease in the CSF hypocretin-1 level occurs in relation to occurrence of clinical symptoms and whether the hypocretin deficiency is a congenital/developmental or an acquired problem as this is critical for understanding the pathogenesis of the disease.

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REFERENCES


