

The CSF Sampling by Lumbar Puncture in Healthy Japanese Elderly Subjects; Age and cultural-specific considerations

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The Methodological Questions Being Addressed

Should any specific considerations have to be taken when CSF samplings were performed in healthy elderly Japanese subjects?

Introduction

Cerebrospinal fluid (CSF) evaluation helps us to understand CNS penetration, PK characteristics, as well as the PK/PD relations of investigational drugs. Therefore, the sampling of CSF became a standard procedure in healthy subjects for the development of a broad range of CNS drugs as part of phase 1 clinical studies worldwide.

However, on the contrast to the fact that about 33 % of a total population in Japan is now over 65 years old and subsequently there is a vast CNS pharmaceutical market in Japan, until recently, CSF sampling by lumbar puncture had been limited to only patients.

From the mid-2010s, healthy elderly studies involving CSF samplings had been carefully considered in Japan, and now the CSF samplings have been established as a procedure that provides vast information in CNS drug developments in Japan.

However, little has been reported about the normal range of the CSF parameters in Japanese, especially in elderly populations. As the normal values of CSF parameters are important in the safety point of view as well as the efficacy evaluation in clinical trials, the values of main CSF parameter in healthy Japanese elderly subjects were investigated in this study on the purpose of setting an age-specific normal reference value for future clinical trials in Japanese populations.

In addition, to evaluate the specific considerations and understand the public perception of CSF sampling in healthy elderly subjects in Japan, surveys were performed before and after the procedure for healthy elderly Japanese male and female subjects.

Methods

- One hundred eighty-four cognitively and physically healthy elderly female and male subjects (age, 50-80 years) participated in clinical studies including CSF sampling conducted at SOUSEIKAI Global Clinical Research Center from 2014 to 2018.
- The CSF samplings were performed by a lumbar puncture by experienced in-house anesthesiologists after a thorough explanation of the procedure to the subjects.
- Safety profiles regarding CSF sampling procedures were recorded.
- The CSF samples of 32 subjects were collected before the study drug administration and the concentration of total protein, glucose, and the number of cells were analyzed (Study 1).
- A survey regarding the participation in clinical studies involving CSF sampling was performed in 506 volunteers using questionnaires (Study 2).
- Another survey regarding the impression of CSF sampling was performed after the CSF sampling procedure in 184 volunteers using questionnaires (Study 3).
- All the CSF sampling procedures were carried out as a part of clinical trials, and the protocols, including the survey studies, were reviewed and approved by SOUSEIKAI Hakata Clinic IRB.

Results

I. Study 1

- The data of 32 subjects (age range, 55-71 years) showed that the glucose levels and the number of cells were within the Japanese adult normal range (Glucose 50-70 mg/dL, Number of cells 0-5 / μ L)(data not shown).
- The mean total protein level was 44.0 ± 14.0 mg/dL (Fig. 1). Sex differences were not observed (Fig. 1).
- 50% of the total subjects showed higher total protein levels than the standard adults' normal range for Japanese¹⁾ (10-40 mg/dL) (Fig. 1).
- Our data were consistent with the results of a recent systematic review in which the increasing total protein levels with advancing age have been reported²⁾ (Fig. 2).

Fig. 1. The Total Protein level in CSF in healthy elderly Japanese subjects

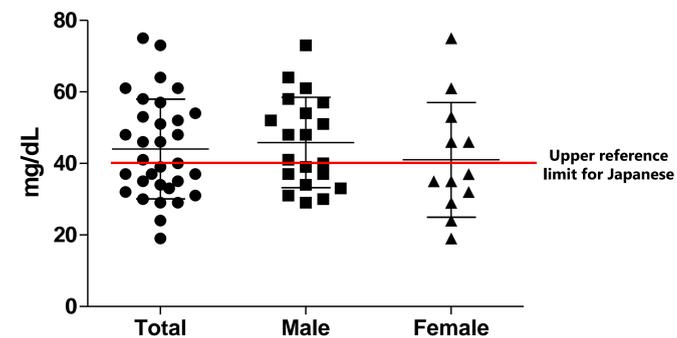


Fig. 2. Correlation between age and total protein level in healthy elderly Japanese subjects.



II. Study 2

Subject surveys regarding CSF sampling

- The survey results indicated that 71% of 506 healthy elderly Japanese subjects are willing to participate in clinical studies involving CSF sampling by Lumbar Puncture. (Male: 75%, Female: 66%). 60% of the 29% of negative responses were from the female subjects.
- The reasons for the "Hesitant" response were mainly "concerns about the adverse events" as we anticipated. Lumbar Puncture, in some cases, seemed to be misunderstood as bone marrow aspirations.

Fig 3. Willingness of the participation Before The Procedure

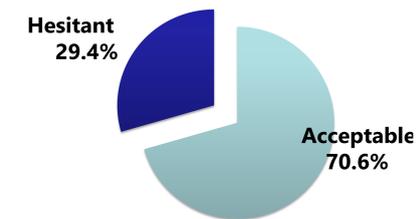
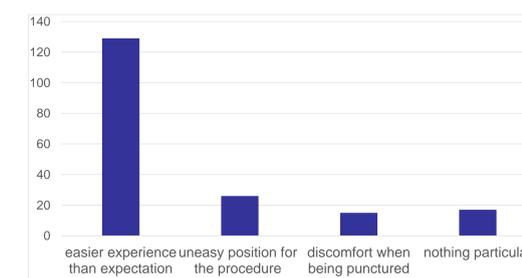


Table 1. Survey Results By Gender And Age

Range of Age	60~69	70~74	over 75	Total
Acceptable	164	137	56	357
Male	78	65	38	181
Female	86	72	18	176
Hesitant	76	47	26	149
Male	42	17	13	59
Female	47	30	13	90
Total	240	184	82	506

III. Study 3

Fig 4. Impression about CSF sampling after the procedure



IV. Safety

- All CSF sampling procedures were completed without any serious adverse events in healthy Japanese elderly subjects in the clinical trial setting.
- Eight (5.4%) headache and 4 (2.7%) heaviness of head were found among 149 subjects when 21G or 22G Quincke needle was used for lumbar puncture.
- Zero (0%) headache and 0 (0%) heaviness of head occurred among 35 subjects when 22G or 24G pencil point needle was used for lumbar puncture.
- All adverse events were not severe and recovered naturally without any treatments.

Results & Discussion

- It was possible to perform CSF samplings by a lumbar puncture safely in healthy Japanese elderly subjects at our facilities.
- Our data suggested that the protein concentration in CSF was higher in elderly subjects than the normal reference CSF values for Japanese adult populations (Fig 1). The appropriate reference values of protein concentration in elderly adults have to be taken into consideration when the procedures are performed in elderly populations in Japan.
- A recent systemic review²⁾ suggested that the upper reference limit should be age-partitioned, and that may be the values over 60 mg/dL at age 50 and above should be applied. A reference range of 15-45 mg/dL has been frequently cited in medical textbooks²⁾, and a reference range of 10-40 mg/dL has been widely used for clinical purposes for the people of all ages in Japan¹⁾. Our data also suggested that the upper reference limit should be reconsidered for elderly populations in Japan.
- Our survey shows that 71% of subjects considered the CSF sampling procedure acceptable (Fig 3), and a large population of subjects answered that the procedure was more comfortable than they had expected (Fig 4).

Conclusions

As current drug development is now becoming more and more necessary to properly test target-aged populations from the early stages of clinical trials, even though the protocol involves invasive procedures, it is possible to conduct the studies safely and efficiently by understanding the subjects' perceptions and the physiological characteristics.

[Reference]

- 1) Kanai's Manual of Clinical Laboratory Medicine, 34 edition, Kanehara Shuppan, 2015.
- 2) Breiner A et al. Adult CSF total protein upper reference limits should be age-partitioned and significantly higher than 0.45 g/L: a systematic review. J Neurol. 2019 Jan 8. doi: 10.1007/s00415-018-09174-z. [Epub ahead of print]

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