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Cerebrospinal Fluid (CSF) Calcium in Neurological Disorders: A Preliminary Report

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Abstract

Routine biochemical analysis of CSF is confined to very limited chemical profile. In general, electrolytes, particularly CSF Ca^{++} analysis have been neglected from diagnostic point of view. The present report discusses the relevance of CSF Ca^{++} level both from the point of diagnosis and prognosis. The observation made in this study also leads to the speculation about the molecular basis of at least some of the CNS disorders.

Key words -

CSF Ca^{++},
Ultrafiltrable Ca^{++},
CNS disorders,
Diagnosis,
Prognosis

Cerebrospinal fluid (CSF) analysis is one of the routine diagnostic approaches available in laboratory medicine whenever the central nervous system (CNS) disorder is suspected. The rationale behind this being, the CSF being in close contact with the nervous tissue should reflect the state of health and disease of the CNS. Available data suggests that the composition of the CSF and extracellular fluid (ECF) in central nervous system are very much similar [2], [7], [8], [10]. The routine chemical examination of CSF is usually confined to a limited profile such as sugar, total protein and a qualitative test for globulins. Of late there has been some interest even to look into certain enzyme profile in neurological disorders [15]. However, among the other constituents of CSF, the electrolytes in general have elicited little interest from diagnostic point of view [1], [4], [8], [23]. In particular, the CSF Ca^{++} is always looked upon as having no diagnostic significance as this divalent cation is said to be 'not affected' by diseases of nervous system [10] although it must be added that there is only limited published data about this aspect. Though there are some reports in literature indicating correlation between CSF Ca^{++} content and clinical status in affective disorders [18], [5], [24] no extensive studies on a large sample have been done to correlate the levels of CSF Ca^{++} in neurological disorders. Limited available literature on this subject [6], [11], [16], [20], [25] suffers from inadequate number of specimens from inadequate number of specimens to arrive at any meaningful conclusion. In view of this, the studies on the levels of CSF Ca^{++} in various neurological disorders was undertaken, and the present communication reports an account of the observations made.

Materials and Methods

The study was carried out on CSF materials referred for routine chemical examination to our Clinical Chemistry section. Samples were subjected to centrifugation to get rid of the cellular elements, and the specimens indicating haemorrhage were excluded from the study. Ca^{++} assay was carried out by methyl thymol dye binding method of Gindler and King [17], and the protein method of Meulemans [21]. Thus more than three hundred CSF samples covering various neurological disorders were analysed, and the results obtained were analysed to find out the interrelationship between the protein and Ca^{++} content of the CSF and also the possible diagnostic relevance of CSF Ca^{++} level in neurological disorders. Patients clinical history and the course of the disease was taken into consideration by referring to the medical records while analysing the results.

Results

CSF Ca^{++} in neurologically normal control group (orthopaedic and gyanec. cases) was found to be 2.05-0.32 mEg/L, and the protein content was within the range of 0.15 g/L to 0.4 g/L. In patients group, it was observed that there was wide-variation in CSF Ca^{++} content among the patient population diagnosed under different neurological disorders. The details regarding the number of samples in each category and the CSF Ca^{++} level, irrespective of protein content is presented in table 1. When the same results were presented as in the form of scatterodiagram, correlating the CSF protein and Ca^{++} (fig.1) at least five different groups became discernable and the same is presented in table 2. Quite a large number of CSF (136 out of 318) samples were found to have a normal protein (0.1 gm to 0.5 g/L) and normal Ca^{++} level (2.11 ± 0.29 mEg/L). Among this group of patients, majority of the cases were diagnostically not confirmed though there were queries about the suspected diseases (table 1). Among the second group wherein normal protein content and high Ca^{++} level was observed, most of the patients had cerebrovascular, neoplastic and demyelinating disorders. A large number of patients in this group had CSF Ca^{++} level above 4 mEg/L extending upto 7.5 mEg/L. There were a small group of patients with neurological disorders of hereditary nature or idiopathic cause whose CSF protein content was found to be normal but very low Ca^{++} level. Among the patients who were diagnosed under infective/inflammatory category there were two distinct subgroups on the basis of CSF protein and Ca^{++} level, namely CSF with

i) high protein with high Ca^{++} and

ii) high protein and normal Ca^{++}.

On going through medical records it was found that the former group (group No. 4 in table 2) constituted most of the tuberculitis meningitis (TBM) and TBM with hydrocephalus whereas the pyogenic meningitis were confined to group No. 5 (table 2). Thus it is of interest to note that there is no correlation between CSF protein and Ca^{++} content in most of the specimens from different patient population contrary to the belief that Ca^{++} in CSF is related to protein content.

Scatterodiagram depicting the interrelationship between CSF protein and Ca^{++} content in neurological

disorders.

Table I - CSF Ca^{++} (irrespective of CSF protein content) in various neurological disorders.

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Table II - Interrelationship between CSF protein and calcium in different types of CNS disorders. Numbers in parenthesis indicate the number of cases analysed in each group.

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Discussion

Calcium in plasma/serum is present both in free and bound (to albumin) state. CSF being a low protein biological fluid, it was believed that under normal circumstances the CSF Ca^{++} essentially represents the ultrafiltrable (free) Ca^{++} of plasma [12], [15]. The reported values of Ca^{++} in normal CSF varies from 2.0-2.8 mEq/L and is comparable with that of ultrafiltrable plasma Ca^{++} [6], [7], [19], [9], [25]. However, the observation that in hyper-parathyroidism, the ultrafiltrable plasma Ca^{++} was greater than CSF calcium and in tetany and in some cases of ureamia and plasma diffusible Ca^{++} was below CSF Ca^{++} [15] support the view that the CSF Ca^{++} does not represent the ultrafiltrable plasma Ca^{++} [12]. Moreover, the experimental studies involving the manipulating of plasma Ca^{++} level did not affect CSF Ca^{++} level [15]. Thus the fact that CSF Ca^{++} does not represent the diffusible plasma Ca^{++}, but is the result of local secretory process [10], [12] makes it an interesting proposition to study the CSF Ca^{++} as a criteria to assess the Ca^{++} metabolism CNS disorders of different etiology. However, it is stated that there is no change in CSF Ca^{++} in epilepsy, parkinsonism or cerebrovascular diseases or in purulent meningitis despite a major increase in protein content [10], [9], [24]. The fact that CSF Ca^{++} is the result of local secretory process [10], [12], [15] rather than reflection of diffusible fraction of plasma Ca^{++}, the CSF Ca^{++}, as a variable factor should reflect the state of metabolic state of CNS and with the concomitant knowledge about protein content should be of great value both from the point of diagnostic and prognostic aspects. Under inflam/infect group of 130 CSF samples (table 1), 45 of them had high protein and normal Ca^{++} and almost all of them were diagnosed clinically as pyogenic meningitis, whereas 58 specimens from the same group had high protein and high Ca^{++} were diagnosed as tuberculosis meningitis (TBM). Thus it is encouraging to note that CSF Ca^{++} along with protein content is useful in differential diagnosis of the meningitis process.

In contrast to the prevailing belief that CSF Ca^{++} is not affected by diseases of nervous system [10], [12] the present study clearly established that the CSF Ca^{++} is highly variable in different neurological

disorders (table 1). Secondly, the data from this study also indicates that CSF Ca^{++} in pathological conditions is independent of the protein content (table 2). In a small group of ten patients having normal protein with low Ca^{++}, six were found to be having disease of hereditary nature. It is worth pursuing studies to understand the biochemical lesion involved in CNS Ca^{++} metabolism in such of those disease of hereditary in nature. CSF with normal protein and high Ca^{++} level group had patients having vascular episodes and degenerative diseases along with diseases of idiopathic in nature. Here, it is significant to note that such of those patients who had vascular episodes with normal protein and CSF Ca^{++} above 4 mEq/L, the prognosis was very poor as revealed in the medical records.

There are reports to indicate that the CSF Ca^{++} remain unchanged in post-mortem specimens unlike $K^{+}$and Mg^{++} [22], and this property has been attributed to the divalent cation's (Ca^{++}) strong affinity to the structural components of the cells [10]. In view of this, the observation made in the present study, i.e., an increase in CSF Ca^{++} in vascular diseases and degenerative diseases, in spite of protein being normal leads to the speculation about the molecular basis of the pathology involved. In this context, we may speculate that the rise in CSF Ca^{++} is secondary to the disease related alteration in the structural integrity of the cellular components leading to the release of cellular Ca^{++} to the ECF which in turn in reflected in CSF. Therefore an increase of CSF Ca^{++} in such situation might reflect the degree of tissue damage. It is obvious that in such cases a routine CSF analysis would have shown a normal biochemical profile but for altered CSF Ca^{++} level, which hitherto considered to have no diagnostic significance. It is worthwhile to have a fresh look at the relevance of CSF Ca^{++} from diagnostic and the molecular aspects of Ca^{++} metabolism in CNS disorders.

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