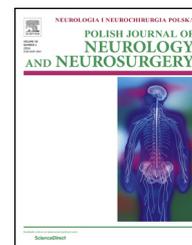


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Original research article

Cerebrospinal fluid ferritin — Unspecific and unsuitable for disease monitoring

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ABSTRACT

Background and purpose: Subarachnoid hemorrhage is sometimes difficult to diagnose radiologically. Cerebrospinal fluid (CSF) ferritin has been proposed to be highly specific and sensitive to detect hemorrhagic central nervous system (CNS) disease. We analyzed here the specificity of CSF ferritin in a large series of various CNS diseases and the influence of serum ferritin.

Materials and methods: CSF ferritin, lactate, protein and total cell count were analyzed in 141 samples: neoplastic meningitis ($n = 62$), subarachnoid hemorrhage ($n = 20$), pyogenic infection ($n = 10$), viral infection ($n = 10$), multiple sclerosis ($n = 10$), borreliosis ($n = 5$) and normal controls ($n = 24$). Cerebrospinal fluid ferritin was measured with a microparticle immunoassay. In addition, serum and CSF ferritin were compared in 18 samples of bacterial and neoplastic meningitis.

Results: In CNS hemorrhage, median ferritin was $51.55 \mu\text{g/L}$ (sensitivity: 90%) after the second lumbar puncture. In neoplastic meningitis, the median CSF ferritin was $16.3 \mu\text{g/L}$ (sensitivity: 45%). Interestingly, ferritin was higher in solid tumors than that in hematological neoplasms. In 90% of pyogenic inflammation, ferritin was elevated with a median of $53.35 \mu\text{g/L}$, while only 50% of patients with viral infection had elevated CSF ferritin. In ventricular CSF, median ferritin was $163 \mu\text{g/L}$, but only $20.6 \mu\text{g/L}$ in lumbar CSF. Ferritin was normal in multiple sclerosis and borreliosis.

Conclusions: Ferritin was elevated not only in hemorrhagic disease, but also in neoplastic and infectious meningitis. Ferritin was not a reliable marker of the course of disease. The influence of serum ferritin on CSF ferritin is negligible. We conclude that elevated CSF ferritin reliably, but unspecifically indicates severe CNS disease.

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1. Introduction

In spite of improvements of computed and magnetic resonance tomography, the diagnosis of hemorrhage affecting the central

nervous system (CNS) still remains difficult in a number of cases, especially when performed more than 6 days after disease onset [1]. Thus, cerebrospinal fluid (CSF) ferritin may be an important biomarker to indicate hemorrhage that reaches the inner or outer CSF spaces. Previous studies reported a high

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sensitivity and specificity of CSF ferritin for CNS bleeding [2-9]. We asked here if ferritin was a suitable marker to discriminate CNS hemorrhage from bacterial and neoplastic meningitis and other acute or subacute diseases of the CNS.

The iron-binding protein ferritin occurs in 20 isoforms in each organ, mainly in liver, spleen and bone marrow. After hemorrhagic events, most tissues synthesize ferritin in order to bind free iron and prevent the occurrence of free radicals that damage tissues. In addition to tissue-building cells, macrophages are among the most potent synthesizers of ferritin. When the excess of iron is too high to be bound, cells are lysed and ferritin released which can be measured in the surrounding body fluid [2,10]. Ferritin levels in different organs correlate with serum ferritin and are elevated not only in cases of hemorrhage, but also in malignant disease [11], and acute or chronic inflammation [12].

Serum ferritin increases in hematological and solid neoplasms, such as hepatocellular carcinoma, pancreatic cancer, lung cancer and neuroblastoma. It correlates with tumor activity and dissemination. Tumor-associated increase of serum ferritin is caused by ferritin synthesis by tumor cells [13] and tumor-tissue disbanding [6].

With its high molecular weight of 450 kD, ferritin does not cross the blood-brain-barrier [3]; yet it is also detected in the CSF of healthy individuals. The physiological level of ferritin in the CNS depends on the iron level in CSF oligodendroglia [14]. Following CNS hemorrhage, ferritin in the CSF increases especially in microglial cells. Ferritin is also one of the immunohistochemical markers of microglia [15].

The standard range of ferritin in the CSF has not yet been well defined. Milman et al. [3] assumed a normal range of CSF ferritin to 2-7 µg/L, Sindic et al. [6] set an upper limit at 5.5 µg/L, and Zappone [9] - at 20 µg/L. In our clinical routine, the upper limit is set at 18 µg/L, according to the publication of Kern et al. [16].

With this relatively high upper limit of CSF ferritin, we assessed the sensitivity and specificity of this surrogate marker in cases of CNS hemorrhage and compared with cases of viral and pyogenic (bacterial and fungal) infection, neoplastic meningitis, multiple sclerosis and controls without pathological CSF findings.

2. Materials and methods

A total of 141 CSF samples were evaluated retrospectively and in part prospectively. The cases were divided into diagnostic

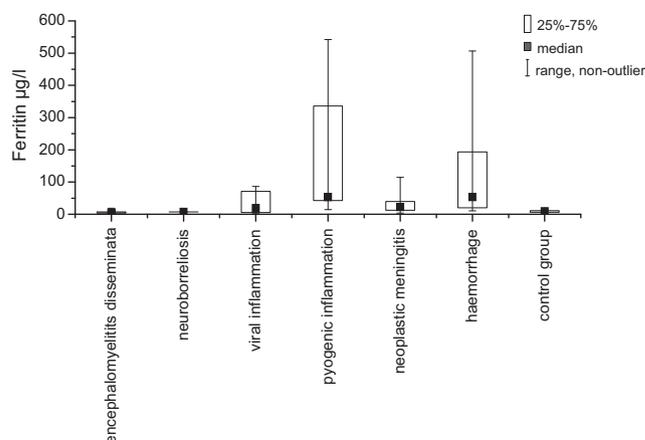


Fig. 1 – Comparison of ferritin concentrations in all diagnostic groups. Center line, median; boxes, 25 and 75% percentiles; vertical lines, total range of values.

groups: normal-pressure-hydrocephalus (NPH, $n = 24$) as a control group without pathological CSF examination, sub-arachnoid hemorrhage ($n = 20$), neoplastic meningitis ($n = 62$), bacterial meningitis ($n = 10$), viral meningitis ($n = 10$), borreliosis ($n = 5$) and multiple sclerosis ($n = 10$). Cerebrospinal fluid levels of ferritin, lactate, total protein and total cell count were determined in our laboratory between 1999 and 2006. In addition, ferritin was measured in 18 paired serum/CSF samples (bacterial meningitis - 5 cases, hemorrhage - 6 cases, gliomas - 2 cases, as well as trauma, amyotrophic lateral sclerosis and headache one each) in order to assess a possible inter-correlation.

Cerebrospinal fluid ferritin was measured with a micro particle enzyme immunoassay (MEIA) AxSYM ABBOTT in undiluted CSF samples. 200 µL of CSF sample was required. The analytic sensitivity of the AxSYM ferritin assay was 1.0 ng/mL.

Cerebrospinal fluid total protein was quantified by a turbidimetric method of sulphosalicylic acid and CSF glucose was quantified with an enzymatic method. Cerebrospinal fluid total cells were counted microscopically in a Fuchs Rosenthal chamber by an experienced technician. For differential cell count and to detect the presence of malignant cells, CSF samples were concentrated by Cytospin. Cerebrospinal fluid samples were protein-enriched with albumin. The slides were

Table 1 – Rate of elevated ferritin, median level, total range, and difference from controls in the diagnostic groups as indicated by p -values. The p -value indicates the level of significance for the difference of ferritin from the control group (Mann-Whitney U -test).

Disease	n	CSF ferritin median (µg/L)	Limit (µg/l)	Values > 18 µg/L	p -Value
Control group	24	9.45	18	0	<0.001
Hemorrhage	20	51.55	18	15 (75%)	
Neoplastic meningitis	62	16.25	18	27 (45%)	0.022
Bacterial meningitis	10	53.35	18	9 (90%)	0.75
Viral meningitis	10	18.85	18	5 (50%)	0.070
Neuroborreliosis	5	7.5	18	0	0.001
Multiple sclerosis	10	6.15	18	1 (10%)	<0.001

CSF, cerebrospinal fluid.

stained by May–Grünwald–Giemsa technique and analyzed by at least two trained researchers (SMA and EN). Cerebrospinal fluid samples with more than 50 erythrocytes/mm³ were excluded.

2.1. Statistical analyses

The correlation between CSF ferritin and the underlying disease was analyzed with the Kruskal–Wallis test, the Mann–Whitney *U*-test and the χ^2 test.

3. Results

3.1. Diagnostic groups

In the control group, median ferritin was 9.45 $\mu\text{g/L}$. All ferritin levels were lower than 18 $\mu\text{g/L}$ (Fig. 1 and Table 1).

In patients with CNS hemorrhage, ferritin was increased above 18 $\mu\text{g/L}$ in 15/20 (75%) patients in the first CSF probe. The median ferritin was 51.55 $\mu\text{g/L}$ and significantly higher than that in the control group ($p < 0.001$; total range 10.8–2170 $\mu\text{g/L}$, Fig. 1 and Table 1). In consecutive examinations, additional 15% of patients had increased ferritin levels.

Differences were seen between lumbar and ventricular ferritin. The median value of ferritin in the ventricular CSF was 163 $\mu\text{g/L}$, while the median lumbar ferritin was only 20.6 $\mu\text{g/L}$.

In neoplastic meningitis, 28/62 (45%) patients had increased CSF ferritin levels with a median of 16.3 $\mu\text{g/L}$ (total range 2.3–792 $\mu\text{g/L}$, not significant). Interestingly, ferritin levels were higher in neoplastic meningitis from solid tumors (median 17.3 $\mu\text{g/L}$) than that in hematological neoplasms (12.5 $\mu\text{g/L}$). The second lumbar puncture revealed additional 10% of cases with elevated ferritin. The median CSF lactate was not elevated, and the intraindividual values did not correlate with CSF ferritin levels.

The highest median ferritin of 53.35 $\mu\text{g/L}$ was found in pyogenic (bacterial and fungal) meningitis, where 9/10 (90%) of patients had elevated ferritin (total range 14.5–542 $\mu\text{g/L}$). In viral meningitis, only 5 of 10 patients had elevated CSF ferritin and the median ferritin was only slightly elevated to 18.85 $\mu\text{g/L}$ (total range 3.9–343 $\mu\text{g/L}$). No elevated values and no increase of median CSF ferritin were seen in patients with borreliosis or multiple sclerosis.

3.2. Comparison between diagnostic groups

The Mann–Whitney *U*-test, but not the χ^2 test, showed that CSF ferritin was significantly higher in cases of hemorrhage as compared with neoplastic meningitis ($p = 0.022$, Table 2).

Levels of CSF ferritin were comparable in hemorrhage and bacterial meningitis. The group of patients with viral inflammation showed an insignificant tendency to lower levels of CSF ferritin in comparison with the hemorrhage group ($p = 0.070$, Kruskal–Wallis; $p = 0.338$, χ^2 test). The frequency of distribution of CSF ferritin as assessed with the Mann–Whitney *U*-test varied in all groups; only the groups of viral inflammation and of neoplastic meningitis had similar distribution ($p = 0.657$). The median value was 22.9 $\mu\text{g/L}$ for the neoplastic meningitis patients and 18.85 $\mu\text{g/L}$ for viral

Table 2 – Cerebrospinal fluid ferritin, lactate, total cell count, total protein and oligoclonal IgG in all diagnostic groups.

	Control group (n = 24)	Neoplastic meningitis (n = 27)	Subarachnoidal hemorrhage (n = 20)	Pyogenic inflammation (n = 10)	Viral inflammation (n = 10)	Encephalomyelitis disseminata (n = 10)	Lyme borreliosis (n = 5)
Ferritin ($\mu\text{g/L}$)							
Median (range)	9,45 (2,1–16,1)	22,9 (4,7–792)	51,55 (10,8–2170)	53,35 (14,5–542)	18,85 (3,9–343)	6,15 (2,6–18,7)	7,5 (6,4–8,6)
Cases above normal	0	16	15	9	5	1	0
Lactate (mmol/l)							
Median (range)	1,7 (1,1–2,5)	2,2 (1,3–9,2)	2,8 (1,6–5)	5,5 (1,8–13,8)	1,8 (1,2–3,2)	1,25 (1–1,9)	1,6 (1,3–3)
Cases above normal	3	12	4	10	2	0	1
Cell count (cells/ μl)							
Median (range)	1 (0–5,0)	19 (0–4693)	12 (1–42)	217 (35–5290)	42,5 (3–475)	7,5 (2–33)	85 (0–504)
Cases above normal	1	19	14	10	1	8	3
Whole Protein (mg/l)							
Median (range)	395,5 (221–1375)	1154 (195–13400)	634 (198–4854)	1971 (768–3592)	676,5 (369–1941)	490 (350–1926)	1004 (396–1660)
Cases above normal	17	21	14	10	3	4	3
IgG							
Pos	5	7	0	2	6	10	3
Neg	19	20	6	8	4	0	0

inflammation. Taken together, ferritin levels in hemorrhagic disease were not significantly higher than that in pyogenic infection or in neoplastic meningitis.

In the group of patients with bacterial meningitis, 2/10 patients had elevated serum (and CSF) ferritin levels. Furthermore, only one patient in the neoplastic meningitis group (1/10) showed a higher level of ferritin in the serum, while CSF ferritin was normal.

4. Discussion

The study presented here analyzed lumbar and ventricular CSF ferritin in hemorrhagic and non-hemorrhagic disease compared with normal controls without known pathology. Lumbar CSF ferritin was most often increased in the second sample in hemorrhagic disease with a high sensitivity of 90%. We found, however, significantly elevated CSF ferritin also in neoplastic and infectious meningitis.

Ferritin as an iron-binding protein that does not cross the blood-brain barrier is most often regarded to be an indicator of hemorrhagic CNS disease. We observed an elevated level of ferritin in serum and CSF at the same time in 3 cases only. In line with previous reports [2–4,6–9], we found significantly elevated ferritin levels following subarachnoid and intracerebral hemorrhage. Interestingly, 25% (2/8) of the results in samples taken up to 3 days after disease onset were false-negative, which resulted in a total of 15% false-negative results in the first samples. Only 1/17 (6%) false-negative results was assessed between 4 and 20 days after the bleeding, leading to a sensitivity of 90% when a second sample was taken in case of a negative first result. In none of the 3 (100%) samples taken 30 or more days after hemorrhage, CSF ferritin was increased, indicating a complete normalization within this time. Accordingly, a maximum of CSF ferritin levels between day 4 and 6 after hemorrhage has been reported previously [2]. Apparently, ferritin does not increase before phagocytosis of erythrocytes or hemosiderin can be detected cytologically, which is assumed to be the case within 12–24 h [17–21]. Cerebrospinal fluid ferritin analysis may therefore be regarded as equally quick and sensitive but unspecific, while the detection of siderophages is highly specific for CNS hemorrhage [22–25].

Of note, ferritin was significantly higher in ventricular than that in lumbar samples. This is most probably an epiphenomenon, since ventricular samples were taken through external drains, which are necessary only in severe intracranial bleeding. Unfortunately, we could not compare lumbar and ventricular samples in the same patient at the same time, since there was no need for a lumbar puncture once a ventricular drainage was applied.

Although associated with a high sensitivity, CSF ferritin cannot be regarded as specific for CNS hemorrhage, since significantly elevated levels are also observed in neoplastic and infectious meningitis [26]. Controls or cases of multiple sclerosis were not associated with elevated CSF ferritin. Thus, CSF ferritin has to be regarded as an unspecific marker of severe CNS pathology, which excludes normal conditions within the CNS. This corresponds to reports from other groups who also found elevated ferritin in these diseases [3,6,9,16,27–29].

The gold standard for the diagnosis of neoplastic meningitis is CSF cytology [30]. In malignant disease, serum ferritin can be elevated through synthesis by tumor cells [13,31] or by tissue lysis [6]. In neoplastic meningitis, an elevation of CSF ferritin has been described previously [9,13,16,29]. Cerebrospinal fluid ferritin was even proposed to be an early marker of malignant CSF involvement [9,13]. In the study presented here, there was only one case of ferritin elevation previous to the cytological detection of malignant cells. The overall sensitivity, however, was only 45%. This may be explained by the fact that one-third of the cases with cytologically proven neoplastic meningitis had normal cell counts. Total cell count was significantly correlated with CSF ferritin in the initial analysis of this group, but not in subsequent samples. Interestingly, ferritin levels in NM from hematological malignancies were not significantly higher than normal controls. These findings may explain that the sensitivity in our series was lower than that in other series which found sensitivities of 69% [29] or even 90% [16]. Taken together, CSF ferritin only occasionally indicates NM in cases of normal cell counts and negative cytology and is not reliable as an early marker of neoplastic meningitis. Although a decrease of ferritin levels after successful intrathecal chemotherapy could be observed in some of our patients, increasing levels were seen in other cases in spite of normalized routine CSF analysis. This makes the value of ferritin as a marker of response of NM to treatment most doubtful.

Inflammatory processes are often associated with necrotic cell death. This may be more pronounced in pyogenic than in lymphocytic infection. The release of ferritin by necrotic cell death may be the source of elevated CSF levels found in infectious disease. In line with other studies [3,6,9,10,13,16,29], CSF ferritin was elevated in 90% of pyogenic (including one fungal) and 50% of viral infections. By contrast, no case of CNS borreliosis was associated with high ferritin levels. Also in chronic inflammatory CNS disease and multiple sclerosis, no elevation of ferritin was detected. This indicates that ferritin is associated with more severe inflammation. Nevertheless, no correlation between total cell count as an indicator of CNS inflammation and ferritin levels was found. Although multiple sclerosis is a disease with loss of mainly oligodendroglial cells which contain a considerable amount of CNS ferritin, no increase of CSF ferritin values was observed. Obviously, oligodendroglial loss is slow enough to enable the cleavage of ferritin from the CSF.

Although a number of patients with degenerative disease were included into the control group, no increase of CSF ferritin was seen. In one previous series, no pathological values were found as well [9], while two other studies occasionally found elevated ferritin [6,16]. Obviously, also in degenerative disease the loss of CNS cells is slow enough to allow for cleavage of ferritin from the CSF.

5. Conclusions

The negative predictive value of normal CSF ferritin values is not sufficient to exclude CNS disease. By contrast, elevated CSF ferritin regularly, but unspecifically indicates severe CNS disease like hemorrhage, neoplastic disease or infection. Of

note, ferritin may take 2–4 days to be elevated and can be false-negative when examined too early. In this series, ferritin was not suitable to monitor the response of neoplastic meningitis to treatment. By such, ferritin may be helpful as an additional diagnostic marker, but always has to be considered in the context of clinical picture and routine CSF analysis.

Conflict of interest

None declared.

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None declared

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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