II-5a　岐阜大学病院神経内科専門外来のご案内

ファール病・関連脳内石灰化症のため受診をお考えの皆様へ

URL: http://www.med.gifu-u.ac.jp/neurology/fahr.html

岐阜大学大学院 医学系研究科
神経内科・老年学分野

HOME　ご挨拶　教室構成　外来診療　受診をお考えの皆様へ　医療関係者の皆様へ　研究　後期研修　Link

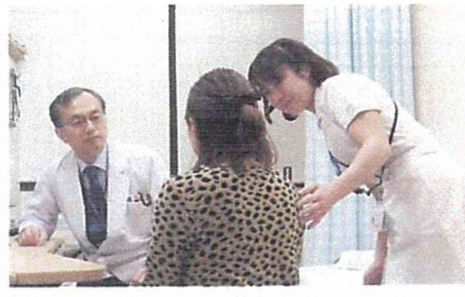
ファール病

受診をお考えの皆様へ
Consultation

HOME＞ファール病・関連脳内石灰化症のため受診をお考えの皆様へ

ファール病・関連脳内石灰化症のため、受診をお考えの皆様へ　Consultation on Fahr's disease or Calcification

是非、御相談ください



- 岐阜大学神経内科・老年科では、「ファール病（特発性大脳基底核石灰化症）の分子病態の解明」研究班の外来窓口を担当しております。
- 「ファール病」、「原因不明の脳内石灰化症」などの診断を受けて、お悩みの方、一度検査を受けたい方、セカンド・オピニオンを受けたい方、遺伝カウンセリングを受けたい方は、遠慮なく、下記へご連絡ください。
- 診断の確認のために、一度は岐阜大学病院の神経内科専門外来受診の予約をとって、受診することをお願いしております。
- 初回診察は一日ですみますが、その後、精査のため一泊入院をお願いすることがございます。

- 担当者：保住 功（客員臨床教授、岐阜薬科大学薬物治療学教授）
- 連絡(予約)方法：
  1. 電話で連絡：　058-230-8121（岐阜薬科大学薬物治療学教授室に直通）
     （不在の際は、お名前と電話番号をお伝えください。折り返しお電話させて頂きます）
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このページの先頭へ ▲

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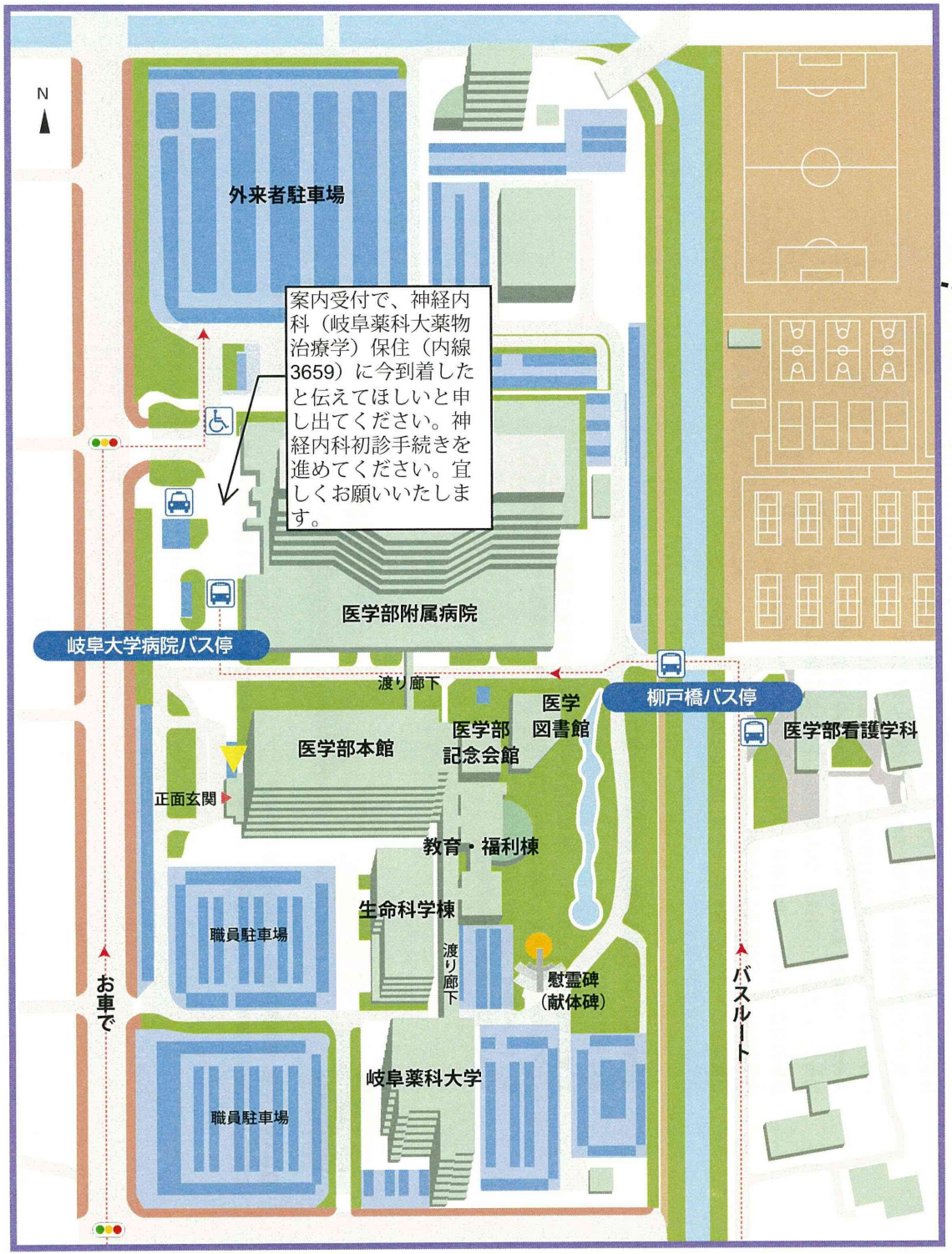


II-5b 診断基準について

暫定的な提案

特発性両側性大脳基底核石灰化症（IBGC）診断基準　（今後の遺伝子検査、生化学的検査のため）

1、　頭部 CT 上、両側基底核に明らかに病的な石灰化を認める。

加齢に伴う生理的石灰化と思われるものを除く（高齢者における淡蒼球の点状の石灰化など）

小脳歯状核の石灰化の有無は問わない。

下記の文献における調査のように、頭部 CT で淡蒼球の石灰化は、約 20%に点状、2~3%に斑状に認め、頻度も加齢とともに増大する傾向があり、年齢を考慮する必要がある。

Yamada M, Asano T, Okamoto K, Hayashi Y, Kanematsu M, Hoshi H, Akaiwa Y, Shimohata T, Nishizawa M, Inuzuka T, Hozumi I. High frequency of calcification in basal ganglia on brain computed tomography images in Japanese older adults. Geriatr Gerontol Int. 2012 Dec 21.

2、　なんらかの進行性の神経症状を呈する

具体的には、頭痛、精神症状（脱抑制症状、アルコール依存等）、精神発達遅延、認知症、パーキンソニズム、不随意運動（PKC 等）、小脳症状など

3、　下記に示すような脳内石灰化をきたす疾患が除外できる

副甲状腺疾患（血清 Ca、P、iPTH が異常値）、偽性偽性副甲状腺機能低下症（Albright 徴候を認める）、ミトコンドリア脳筋症、Cockayne 症候群、Aicardi-Goutières 症候群、Down 症候群、膠原病、血管炎、感染（HIV 脳症等）、中毒、外傷などを除外する。

他に文献上、稀なものとして、炭酸脱水酵素 II 欠損症、Hallervorden-Spats 病、oculodentodigital dysplasia(ODCC)、lipoid proteinosis、Nasu-Hakola 病、Moebius 症候群、Alexander 病などがある。

4、家族歴のある症例ないし *SLC20A2* 等の原因遺伝子異常が判明した症例は症状、画像所見を問わず FIBGC に分類する。

注

・上記診断基準においては、初老期に前頭・側頭型の認知症をきたす小阪・柴山病（DNTC）との鑑別ができないが、確定診断は病理診断に基づき、原因遺伝子やバイオマーカーが確定しない現状においては、分類が困難な症例も多く、あえて区別しない。ただし、DNTC 疑いありの注釈を添える。

・家族例においては、近年、約 4 割で、リン酸トランスポーターである PiT-2 等の遺伝子 *SLC20A2* の変異が判明し、FIBGC は 1~4 型に分類されており、他疾患の可能性も踏まえ、遺伝子検査が望まれる。

参考資料

Familial Idiopathic Basal Ganglia Calcification (FIBGC)の診断基準の日本語訳

1、両側基底核石灰化

2、進行性の神経症状

3、生化学的異常を認めない

4、感染、中毒ないし外傷の原因がない

5、家族歴

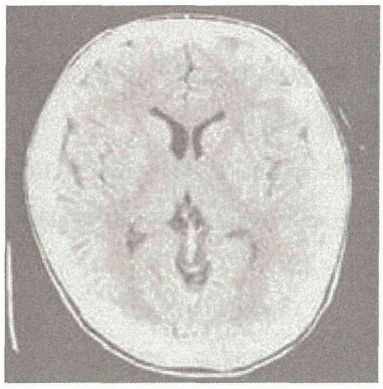
特定疾患案　（患者救済用）

特発性両側性大脳基底核石灰化症（IBGC）診断基準

1、頭部 CT 上、両側基底核に明らかに病的な石灰化を認める。

（加齢に伴う生理的石灰化と思われるものを除く、小脳歯状核の石灰化の有無は問わない）

画像所見の図示



2、日常生活に介助を要する進行性のなんらかの神経症状を認める（中等~重症例）。

具体的には、頭痛、精神症状（脱抑制症状、アルコール依存症等）、精神発達遅延、認知症、パーキンソニズム、不随意運動（PKC 等）、小脳症状など

3、臨床所見から下記に示す脳内石灰化をきたす疾患が除外できる（除外診断）。

・　副甲状腺疾患（血清 Ca、P、iPTH の測定は必須）　　あり　　なし

・　偽性偽性副甲状腺機能低下症（Albright 徴候を認める）　　あり　　なし

（円形顔貌、短躯、第 4 中手骨・中足骨の短縮や皮下骨腫、肥満などを認める）

・　ミトコンドリア脳筋症　　あり　　なし

（低身長、知能低下、筋力低下、難聴、嘔吐、皮質盲、痙攣などを認める）

・　コケイン症候群　　あり　　なし

（低身長、低体重、小頭症、白内障、網膜色素変性症、難聴、日光過敏症、精神運動発達遅滞などを認める）

・　アイカルディ・ゴーティエ症候群　　あり　　なし

（小頭症、痙縮、ジストニア姿勢、高度の精神発達遅延などを認める）

・　Down 症候群　　あり　　なし

（低身長、肥満、知的障害、特異的顔貌、先天性心疾患、先天性白内障、眼振、斜視、屈折異常、難聴などを認める）

・　膠原病、血管炎、感染（HIV 脳症等）、中毒、外傷　　あり　　なし

4、　遺伝子検査

SLC20A2 の遺伝子変異　　あり　　なし

他の遺伝子変異の検索（　　）　　あり　　なし

注　必須ではないが、鑑別上、望まれる。

II-5 c　患者さんへの e メール通信

＃平成 23 年度班会議後の通信

　　様

ご健勝にて過ごしのことと存じ上げます。
平成 24 年 2 月 4 日岐阜にてファ-ル病(特発性両側性大脳基底核・小脳歯状核石灰化症)班会議が開催され、全国から著名な先生方が集合し、盛んな検討が行われ、参加者からは総括的、総合的な検討がなされているという高い評価を頂きました。平成 24 年 2 月 12 日　世界的超一流誌「ネイチャー・ジェネティックス」に家族性ファール病の患者さんからリン酸輸送蛋白の異常が見つかったという論文が、中国から発表されました。これはすべての患者様に同じ異常があるということではないですが、“原因がわからない病気”“治療法がない病気”と言う時代は終わったという印象です。研究、薬物治療開発はまさに緒に就いた所で、これから大いに発展してゆくと思います。
今後ともどうぞ宜しくお願いを申し上げます。
何かございましたら、ご連絡ください。

ファ-ル病研究班
保住　功

＃平成 24 年度班会議後の通信

　　様

　花だよりが聞かれる季節になりましたが、いかがお過ごしでしょうか。
先だって平成 25 年 2 月 2 日(土) 岐阜薬科大学にて班研究の会議が開催されました。
　これまで患者さんの全国からの登録数は 180 名です。その中には殆ど無症状で、それまで脳内の石灰化もわからず、偶然頭部 CT で見つかった方もおられます。全国にはその数の数倍の患者さんがおられると推測されます。決して稀な病気と言うわけではないと思います。
　班研究よる研究で、患者さんの中で、リン酸を運搬するタンパク質の異常がみつかり、それが原因である可能性も考えられ、この発見は治療薬の開発の糸口になるものです。
　またそのたんぱく質の異常が見つからなくても、患者さんの iPS 細胞を作ることで、細胞を用いて病気と同じような状態を作ることができます。
これもまた大いに治療薬の開発へつながります。
　今後、患者さんへの医療情報提供、患者さん同士の情報交換を考えた患者会の育成、医療費が軽減される「特定疾患」としての取り扱いへの申請も考えていきたいと思います。
　お悩みのこと、病気について聞きたいこと、またご意見などございましたら下記へご連絡ください。今後もどうかお体を大切にお過ごしください。

ファール病研究班（班長）
保住　功
連絡方法
１、E-mail: hozumi@gifu-pu.ac.jp
２、お手紙：〒501-1196 岐阜市大学西 1-25-4　岐阜薬科大学　薬物治療学研究室
３、Tel&Fax: 058-230-8121(直通)
（お電話を頂いた時、あいにく不在や不都合な際は、ご用件を伺い、再度こちらからお電話させて頂きますことを予めご了解ください。）

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍：なし

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hozumi I, Kohmura A, Kimura A, Hasegawa T, Honda A, Hayashi Y, Yamada M, Sakurai T,Tanaka Y, Satoh M, Inuzuka T.	High Levels of Copper, Zinc, Iron and Magnesium, but not Calcium, in the Cerebrospinal Fluid of Patients with Fahr's Disease.	Case Rep Neurol	2	46-51	2010
Hozumi I, Hasegawa T, Honda A, Ozawa K, Hayashi Y, Hashimoto K, Yamada M, Koumura A, Sakurai T, Kimura A, Tanaka Y, Satoh M, Inuzuka T.	Patterns of levels of biological metals in CSF differ among neurodegenerative diseases.	J Neurol Sci	303	95-99	2011
Yamada M, Asano T, Okamoto K, Hayashi Y, Kanematsu M, Hoshi H, Akaiwa Y, Shimohata T, Nishizawa M, Inuzuka T, Hozumi I.	High frequency of calcification in basal ganglia on brain computed tomography images in Japanese older adults.	Geriatr Gerontol Int	Dec 21		2012
堀田みゆき 保住　功	希少神経難病ファール病3例の患者と家族のインタビューから得られたもの	臨床看護	38(13)	1907-1912	2012
保住　功	進むFahr病の病態解明	医学のあゆみ	243(4)	323-324	2012
Takagi M, Ozawa K, Yasuda H, Douke M, Hashimoto K, Hayashi Y, Inuzuka T, Hozumi I.	Decreased bioelements content in the hair of patients with Fahr's disease (Idiopathic bilateral calcification in the brain).	Biol Trace Elem Res	151(1)	9-13	2013
Hozumi I.	Roles and Therapeutic Potential of Metallothioneins in Neurodegenerative Diseases.	Curr Pharm Biotechno	in press		2013

Ⅳ. 研究成果の刊行物・別冊

Case Reports in Neurology
Case Rep Neurol 2010;2:46–51
DOI: 10.1159/000313920
Published online: May 7, 2010

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www.karger.com/crn

High Levels of Copper, Zinc, Iron and Magnesium, but not Calcium, in the Cerebrospinal Fluid of Patients with Fahr's Disease

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Tatsuya Hasegawa[b] Akiko Honda[c] Yuichi Hayashi[a]
Kazunori Hashimoto[a] Megumi Yamada[a] Takeo Sakurai[a]
Yuji Tanaka[a] Masahiko Satoh[c] Takashi Inuzuka[a]

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Key Words
Fahr's disease · Calcification · Copper · Zinc · Dementia · Parkinsonism

Abstract
Patients with marked calcification of the basal ganglia and cerebellum have traditionally been referred to as having Fahr's disease, but the nomenclature has been criticized for including heterogeneous etiology. We describe 3 patients with idiopathic bilateral striatopallidodentate calcinosis (IBSPDC). The patients were a 24-year-old man with mental deterioration, a 57-year-old man with parkinsonism and dementia, and a 76-year-old woman with dementia and mild parkinsonism. The former 2 patients showed severe calcification of the basal ganglia and cerebellum, and the latter patient showed severe calcification of the cerebellum. We found significantly increased levels of copper (Cu), zinc (Zn), iron (Fe) and magnesium (Mg), using inductively coupled plasma mass spectrometry in the CSF of all these 3 patients. The increased levels of Cu, Zn, Fe and Mg reflect the involvement of metabolism of several metals and/or metal-binding proteins during the progression of IBSPDC. More numerous patients with IBSPDC should be examined in other races to clarify the common mechanism of the disease and to investigate the specific treatment.

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Introduction

Mild calcification of the basal ganglia is sometimes seen, especially in the elderly. Some patients with marked calcification of the basal ganglia and cerebellum have been reported to be associated with hypoparathyroidism. Most other idiopathic cases have traditionally been referred to as having Fahr's disease, but the nomenclature has been criticized for including a heterogeneous etiology and the disease has presented as a clinically complex syndrome. The patients have not been clearly demonstrated to exhibit any endocrine, metabolic or genetic disorder [1, 2]. The pathophysiological mechanism remains to be elucidated and there is no clue for the treatment. The disease is thus being referred to by some as idiopathic bilateral striatopallidodentate calcinosis (IBSPDC). Inductively coupled plasma mass spectrometry (ICP-MS) can measure the levels of several metals in a small amount of CSF [3]. We have measured those of Japanese patients with IBSPDC to clarify the pathophysiological features of the disease.

Case Reports

Patient 1

A 24-year-old man was hospitalized for gait and speech disturbance. He had been diagnosed with Fahr's disease when 15 years old in a hospital and his IQ was 79. On admission, neurological examination revealed mental deterioration (IQ 69), exaggerated deep tendon reflexes, mild rigidity on the right, and limb and truncal ataxia. CT showed a striking high density area in the basal ganglia and dentate nuclei and revealed progression with age (fig. 1a). No abnormal findings were detected in the blood tests including metals [calcium (Ca), iron (Fe), copper (Cu), zinc (Zn), magnesium (Mg) and manganese (Mn)], in Ca metabolism including parathyroid hormone and the Ellsworth-Howard test, and in routine CSF studies.

Patient 2

A 57-year-old man was hospitalized for dementia, bradykinesia, and gait disturbance. He showed parkinsonism at age 50 and mental deterioration since age 55. Neurological examination revealed dementia, slurred speech, limb ataxia, rigidity, bradykinesia and truncal ataxia. Interestingly, L-DOPA led to a slight improvement in symptoms. He showed similar CT findings as patient 1 (fig. 1b), diabetes mellitus, and no other abnormal findings either in the above-mentioned tests.

Patient 3

A 76-year-old woman came to our hospital for dementia. Neurological examination revealed dementia and mild parkisonism. CT showed a striking high density area in the dentate nuclei, and a moderate area in the basal ganglia and border of the cortex and white matter of the parietal lobe (fig. 1c). No abnormal findings were detected in the above-mentioned tests.

None of the 3 patients had a skeletal structural abnormality or a family history of IBSPDC. Analysis of the levels of Ca, Fe, Cu, Zn, Mg, and Mn in the scalp hair showed no specific findings in the 3 patients using a commercially-available ICP-MS method (La Belle Vie Inc., Tokyo, Japan).

Metals in CSF Analysis

CSF samples were obtained from 3 patients with IBSPDC and 15 controls (9 females and 6 males, age from 22 to 81 years with a mean of 52 years). CSF samples were nebulized with perhydroxyl-nitrate, and the levels of metals (Fe, Cu, Zn, Mg, and Mn) were measured using ICP-MS (HP4500, Agilent Technologies, Japan). Scandium (Sc), yttrium (Y) and thallium (Tl) were added to samples as internal standards. The concentrations of the elements were normalized by the internal standards. The level of

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Ca in the CSF was measured by colorimetry using o-cresolphthalein-complexone (o-CPC) for appropriate means. This study was approved by the Ethics Committee of the Gifu University Graduate School of Medicine.

Results

The levels of Cu, Zn, Fe, and Mg were significantly increased by 3.7, 2.5, 1.9, and 1.6 times of control levels, respectively. Statistical analysis using Mann-Whitney U test showed significant difference ($p < 0.01$) in the levels of Cu, Fe and Mg, and significant difference ($p < 0.05$) in that of Zn, but the levels of Ca (1.1 times) and Mn (0.9 times) in the CSF of all 3 cases with IBSPDC were not significantly different from those of controls (table 1 and fig. 2)

Discussion

Chemical analyses of brain stones in the striopallidodental system has shown high levels of Ca and other metals, such as Fe, Mg, Cu, Zn, Mn, lead, and aluminium [4, 5]. However, there is no apparent explanation for the accumulation of calcium and other metals. The pathophysiological features of Fahr's disease thus remain to be elucidated. The term 'Fahr's disease' has various entities including familial and secondary cases. As the concept of Fahr's disease may encompass diseases derived from different genetic or environmental etiologies in the region, we prefer the term 'IBSPDC' to 'Fahr's disease'. In Japan, elderly patients with dementia and calcification of the basal ganglia were reported to show diffuse neurofibrillary tangles and absence of senile plaques in the pathology [6, 7]. Patients 2 and 3 are considered to be included in this category. We presented 3 clinically idiopathic cases of IBSPDC with variable clinical characteristics and ages.

ICP-MS can measure the level of several metals in a small amount of CSF (less than 1 ml). ICP-MS is more sensitive and accurate than traditional colorimetery and the atomic absorption spectrophotometry method for the measurement of several metals such as Cu, Zn, Mg, except for that of Ca.

Generally, the high density of the basal ganglia and cerebellum in CT images has been thought to be mainly associated with calcification. However, a disorder of Ca metabolism has not been demonstrated in IBSPDC. Only one preliminary study reported rather decreased levels of Ca in the CSF in Fahr's disease, contrary to our expectations [8]. Our 3 cases with IBSPDC showed various ages and clinical presentation, but a similar and significant increase in Cu, Zn, Fe and Mg. This suggests that some cases with IBSPDC are associated with a disorder including heavy metals, especially Cu, Zn, and Fe metabolism, and some metal-binding proteins. Even at low levels, Fe and Cu can catalyze a Fenton reaction, producing highly reactive hydroxyl radicals. Excessive amounts of Cu can be a directly neurotoxic factor and also damage neurons by producing reactive oxygen in neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [9–11].

Pathological and biochemical analyses at autopsy are needed for further evaluation. In the study we could not recognize whether metals in the CSF are free or are derived from metal-binding proteins such as superoxide dismutase-1 and metallothioneins (MT). The high levels of metals in the CSF do not necessarily reflect correctly the pathophysiological mechanisms in the brain; however, this feature of the CSF provides some novel aspects of

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the diseases. CSF of more numerous and clinically variable cases with IBSPDC should be examined in other races to clarify the common pathophysiological features.

We have detected high levels of Cu, Zn, Fe and Mg in the CSF of 3 patients with IBSPDC in Japan. There is no specific and effective treatment for IBSPDC at present, and the progression of the disease is accelerated with age. MT is a small (7 kDa), metal-binding (4 Cu and 3 Zn per molecule) protein that scavenges reactive oxygen species [10]. The study of CSF may provide a clue regarding a common pathway of IBSPDC including the metabolism of Cu, Zn, Fe and Mg and appropriate treatments including metal-chelating agents such as ammonium tetrathiomolybdate, a Cu-chelating agent [11], and metal-binding proteins such as MT [10].

Disclosure

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Table 1. Levels of metals in CSF

	Age	Ca (mg/l)	Mg (mg/l)**	Fe (μg/l)**	Cu (μg/l)**	Zn (μg/l)*	Mn (μg/l)
Patient 1	26	45.0	49.1	418	33.9	8.00	2.10
Patient 2	58	42.0	47.3	461	38.0	10.0	1.00
Patient 3	76	49.0	48.2	458	40.1	22.2	2.10
Average ± SD	53.3 ± 25.3	45.3 ± 3.51	48.2 ± 0.90	446 ± 23.7	37.3 ± 3.15	13.4 ± 7.69	1.73 ± 0.635
Control (n = 15)							
Average ± SD	48.4 ± 22.2	41.1 ± 4.64	29.6 ± 6.52	238 ± 54.7	10.2 ± 2.07	5.30 ± 3.31	1.90 ± 0.971

The levels of Ca, Fe, Cu, Zn, Mg, and Mn in CSF of patients and controls (n = 13). Statistical analysis was performed using Mann-Whitney U test.
* Significant difference, $p < 0.05$. ** Significant difference, $p < 0.01$.

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Fig. 1. CT findings in patients. **a** CT findings in patient 1. A sagittal view shows a striking high density area in the basal ganglia and the dentate nuclei of the cerebellum. **b** CT findings in patient 2. An axial view shows a marked high density area in the basal ganglia and spots at various sites such as the pulvinar thalami, the subcortical area in the frontal lobe, and the border area of the cortex and white matter in the occipital lobe. **c** CT findings in patient 3. An axial view shows a striking high density area in the dentate nuclei of the cerebellum.

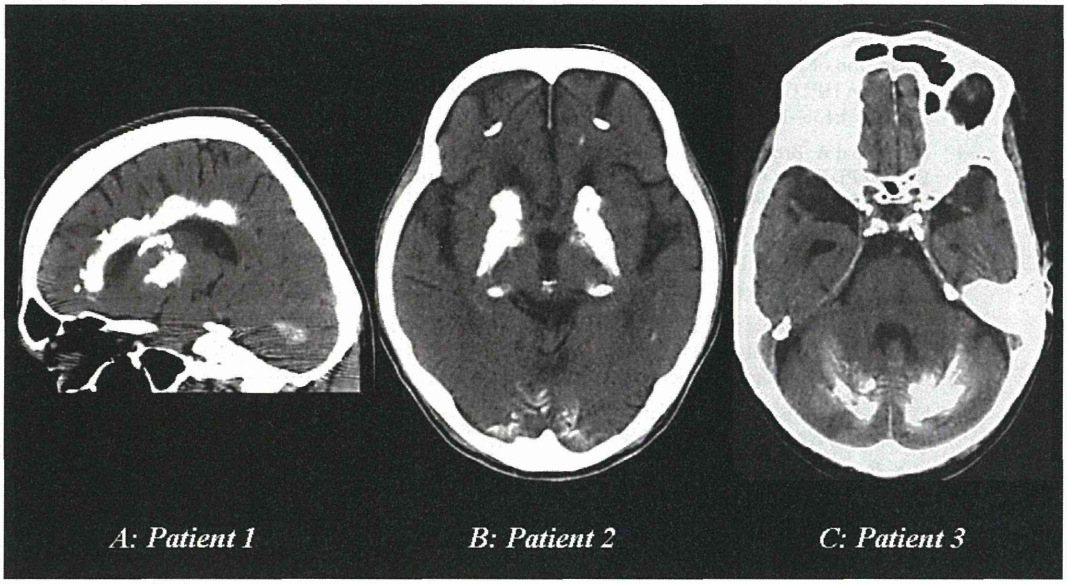
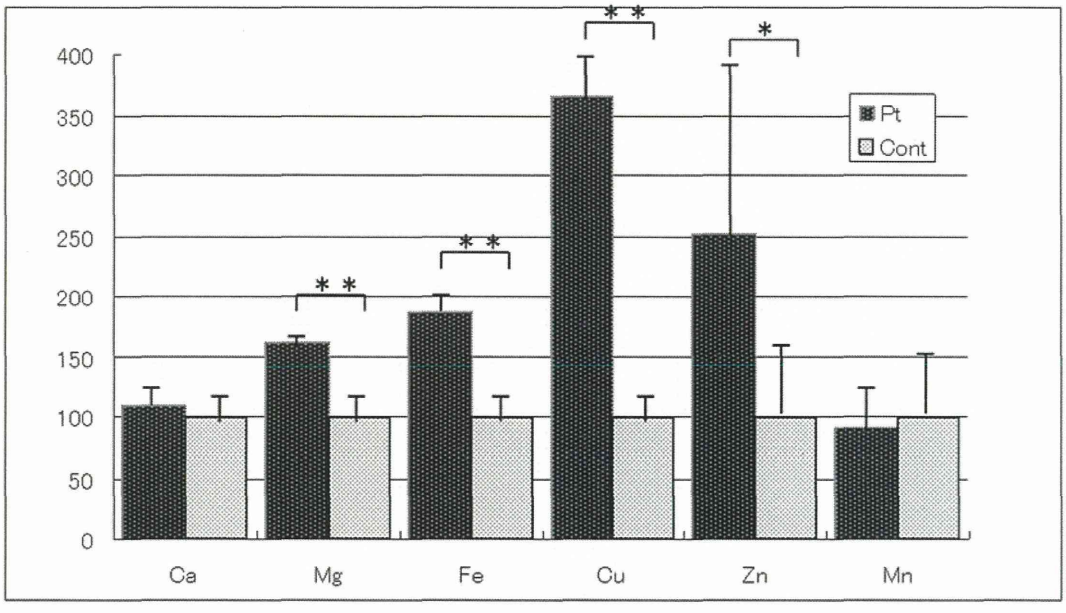


Fig. 2. Comparative values of metals in the CSF. The average levels of Ca, Fe, Cu, Zn, Mg, and Mn in the CSF of patients and controls are shown to be set at the value of 100 (%) in the figure. Especially the values of Cu and Zn in patients are markedly higher compared to those of controls. * Significant difference, $p < 0.05$. ** significant difference, $p < 0.01$.



References

1 Oppenheimer DR, Esiri MM: Calcification of the basal ganglia; in Adams JH, Duchen LW (eds): Greenfield's Neurology, ed 5, Oxford University Press, 1992, pp 1005–1007.

2 Manyam BV: What is and what is not 'Fahr's disease'. Parkinson Relat Disord 2005;11:73–80.

3 Gellein K, Roos PM, Evje L, Vesterberg O, Flaten TP, Nordberg M, Syversen T: Separation of proteins including metallothionein in cerebrospinal fluid by size exclusion HPLC and determination of trace elements by HR-ICP-MS. Brain Res 2007;1174:136–142.

4 Löwenthal A, Bruyn GW: Calcification of the striopallidodentate system; in Vinken PJ, Bruyn GW (eds): Handbook of Clinical Neurology, vol 6, Amsterdam, North-Holland, 1968, pp 703–725.

5 Smeyers-Verbeke J, Michotte Y, Pelsmaeckers J, Löwenthal A, Massart DL, Dekegel D, Karcher D: The chemical composition of idiopathic nonarteriosclerotic cerebral calcifications. Neurology 1975;25:48–57.

6 Shibayama H, Kobayashi H, Nakagawa M, Yamada K, Iwata H, Iwai K, Takeuchi T, Mu-Qune X, Ishihara R, Iwase S, Kitoh J: Non-Alzheimer non-Pick dementia with Fahr's syndrome. Clinical Neuropathol 1992;11:237–250.

7 Kosaka K: Diffuse neurofibrillary tangles with calcification: a new presenile dementia. J Neurol Neurosurg Psychiatery 1994;57:594–596.

8 McLellan TL, Manyam BV, Wilmington DE, Philadelphia PA: Diagnostic implications of CSF calcium measurement. Neurology 1984;34(suppl 1):198.

9 Harris ED: Basic and clinical aspects of copper. Crit Rev Clin Lab Sci 2003;40:547–586.

10 Hozumi I, Asanuma M, Yamada M, Uchida Y: Metallothioneins and neurodegenerative diseases. J Health Science 2004;50:323–331.

11 Tokuda E, Ono S, Ishige K, Naganuma A, Ito Y, Suzuki T: Ammonium tetrathiomolybdate delays onset, prolongs survivals, and slows progression of disease in a mouse model for amyotrophic lateral sclerosis. Exper Neurol 2008;122–128.

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Patterns of levels of biological metals in CSF differ among neurodegenerative diseases

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ABSTRACT

We measured the levels of some biological metals: copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), and zinc (Zn) in the cerebrospinal fluid (CSF) in patients with neurodegenerative diseases (52 patients with amyotrophic lateral sclerosis (ALS)), 21 patients with Alzheimer's disease (AD), and 20 patients with Parkinson's disease (PD) by inductively coupled plasma mass spectrometry (ICP-MS). The diagnoses were additionally supported by neuroimaging techniques for AD and PD. In ALS, the levels of Mg ($p<0.01$ significant difference), Fe, Cu ($p<0.05$), and Zn ($p<0.10$) in CSF were higher than those in controls. Some patients showed very high levels of Cu and Zn before the critical deterioration of the disease. In AD, the levels of Cu and Zn in CSF were significantly higher in patients with late-onset AD ($p<0.01$). In PD, we found significantly increased levels of especially Cu and Zn in particular ($p<0.01$) and Mn ($p<0.05$) in CSF. A multiple comparison test suggested that the increased level of Mg in ALS and that of Mn in PD were the pathognomonic features. These findings suggest that Cu and Zn in particular play important roles in the onset and/or progression of ALS, AD, and PD. Therefore, Cu-chelating agents and modulators of Cu and Zn such as metallothionein (MT) can be new candidates for the treatment of ALS, AD, and PD.

1. Introduction

Biological metals such as copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), and zinc (Zn) have been considered to play very important roles in the progression of some neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1–3]. However, the roles and the metabolisms of such metals remain to be elucidated. Not only the direct toxicity of metals but also the oxidative stress via metals, and metal-associated enzymes and transcription factors modify the progression and diversity of the neurodegenerative diseases. Recently, we have found significantly increased levels of Cu, Zn, Fe, and Mg in the cerebrospinal fluid (CSF) of three patients with 'Fahr's disease' (idiopathic bilateral striato-pallido-dentate calcinosis (IBSPDC), its nomenclature remains controversial) by highly sensitive inductively coupled plasma mass spectrometry (ICP-MS) [4].

Recently, the diagnoses for neurodegenerative diseases such as AD and PD have been more accurate than before using the neuroimage techniques such as magnetic resonance imaging (MRI) with a quantitative analytical method [5], positron emission tomography (PET) or ^{99m}Tc-ethyl cysteinate dimmer-(ECD)-single photon emission computed tomography (SPECT) with quantitative analyses [6], and metaiodobenzylguanidine (MIBG)-cardioscintigraphy with quantitative measurements [7].

Some metals have been thought to be associated with the onset and/or progress of neurodegenerative diseases; Cu, Zn, and Fe for AD, Fe for PD, and Cu and Zn for familial ALS [1]. The mutations of superoxide dismutase 1 (SOD 1) including Cu and Zn in mice cause ALS [8]. Recently, the development of methods of measuring metals has progressed such as ICP-MS [4,9]. With this development, it is possible to clarify the molecular mechanisms underlying the development of neurodegenerative diseases and identify implicated metalloproteins and enzymes. In this situation, it is important to measure accurately the levels of metals in CSF of patients with ALS, AD, and PD using ICP-MS. We speculate on the molecular mechanisms and the roles of metals in neurodegenerative diseases, and develop new therapeutic strategies on the basis of the metal metabolism.

We measured the levels of some biological metals including Cu, Fe, Mg, Mn, and Zn in the CSF of 52 patients with ALS using ICP-MS. We compared the measured values with other clinical data including the subtypes, duration, and the levels of the metals in the serum in the patients with ALS. In addition, we had examined the levels of the

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heavy metals in the CSF of patients with typical features of AD and PD using neuroimaging techniques, and the pathognomonic patterns of neurodegenerative diseases were analyzed by a multiple comparison test.

2. Methods

2.1. CSF sample collection

We obtained samples of the CSF from 52 patients with ALS, 21 patients with AD, and 20 patients with PD. All the patients with ALS fulfilled the revised El Escorial criteria [10] for clinically definite and probable ALS (mean age 65.1 ± 1.6, 28 cases, classical type, 22 cases, bulbar type; and 2 cases, familial type; 17 females and 35 males). We chose samples from patients with AD diagnosed on the basis of the Diagnostic and Statistical Manual for Mental Disorders (4th ed. DSM-IV) [11]. Patients were selected on the basis of both MRI and SPECT findings (n = 21; 7 early-onset type and 14 late-onset type; 8 females and 13 males) to rule out other dementia such as vascular dementia and frontotemporal dementia [5,6]. We excluded patients with abnormal MIBG findings from the AD group to rule out Lewy body disease. We chose 20 patients (11 females and 9 males) with PD diagnosed on the basis of the criteria of British Brain Bank [12] and supported by MRI, ECD-SPECT, and MIBG-cardioscintigraphy to rule out other types of parkinsonism, such as drug-induced parkinsonism and progressive supranuclear palsy. Fifteen patients (9 females and 6 males) with unspecific neurological diseases were used as controls in the study. The first CSF samples that were obtained after the diagnosis were analyzed in this study. The study was approved by the Ethics Committee of the Gifu University Graduate School of Medicine.

2.2. Metals in CSF analysis

The CSF samples were moistly powdered to ash with perhydroxyl-nitrate, and the levels of metals (Cu, Fe, Mg, Mn, and Zn) were measured at least twice using ICP-MS (HP4500, Agilent Technologies, Japan) as previously described [4].

2.3. Statistical analyses

Data were statistically analyzed between disease groups and the control group using the Student's *t*-test. The correlations between the levels of metals in the CSF and other clinical data were analyzed using Pearson Product Moment correlation. Clinical data include age, time between the CSF examination and the disease onset, serum Cu and Zn levels, severity (mini-mental state examination (MMSE) in AD), and the clinical disease subtypes. Correlation coefficients >0.70 were considered significant. Multiple comparisons among disease groups were analyzed using Tukey's honestly significant difference (HSD) test. A significant level of 0.05 was used for all statistical tests (two-tailed). Statistical analyses were performed using IBM SPSS Statistics Base 18.

3. Results

The levels of Cu, Zn, Fe, and Mg in the CSF in patients with ALS, AD, and PD, and controls are shown in Table 1.

In ALS patients, the levels of Cu, Fe ($p<0.05$), and particularly Mg ($p<0.01$) were significantly higher in the CSF of the patients with ALS, and those of Zn were slightly elevated ($p<0.10$) than those in the controls. The data on Cu and Zn in ALS patients, were very widely scattered, because 2 patients had very high levels of Cu (>49.1 ng/ml: > the mean level in ALS + 2 SD) and 3 patients had very high levels of Zn (> 33.5 ng/ml: > the mean level in ALS + 2 SD) in the study. Interestingly these 5 patients with very high levels of Cu and Zn had underwent gastrostomy or tracheostomy within 6 months after the spinal tap in the clinical follow-up research, although all the patients who underwent gastrostomy or tracheostomy within 6 months after the spinal tap did not necessarily show high levels of Cu or Zn. A follow-up study revealed that the patients showed transiently very high levels of Cu or Zinc in CSF (data not shown). Then, we classified 50 ALS patients (exclusion of 2 patients with the familial type) according to the clinical subtypes: classical type (n = 28) and bulbar type (n = 22), and rapidly progressive types (n = 25) and slowly progressive types (n = 25) (data not shown). The patients with the rapid progressive type are those who underwent gastrostomy or tracheostomy, or who died within 2 years of the onset of the disease. No significant correlation was detected between two types. The analyses using Pearson's chi-square test supports the notion that the bulbar type is also generally the rapidly-progressive type ($p<0.01$). We show the levels of biological metals in the CSF in ALS patients in Fig. 1.

Table 1
Levels of metals in the CSF of patients with ALS, AD, and PD. The levels of Cu, Fe, Mg, Mn, and Zn in CSF of patients and controls (n = 15). Fifty patients with ALS (except familial type (n = 2)) are divided into classical type (n = 28) and bulbar type (n = 22). The patients with AD are divided into two groups: early-onset type (the onset is below 65 years) (n = 7), and late-onset type (the onset is at 65 and over 65 years) (n = 14). Statistical analysis was performed using the Student's *t*-test. Significant difference, ** $p<0.01$, * $p<0.05$, + $p<0.10$.

Cont and Pt		Age	Cu	Fe	Mg	Mn	Zn
		years	ng/ml	ng/ml	μg/ml	ng/ml	ng/ml
Cont	Av	48.4	10.2	238.0	29.6	1.9	5.3
(n = 15)	S.D	22.2	2.1	54.7	6.5	1.0	3.3
ALS	Av	65	19.5*	282.5*	35.9**	2.2	11.1 + 11.2
(n = 52)	S.D	11.7	14.8	74.9	4.8	1.5	
Classical	Av	64.6	18.3	276.8	35.2	2.2	12.7
(n = 28)	S.D	10.6	9.3	74.7	5.1	1.4	13.0
Bulbar	Av	67.7	21.0	285.9	36.6	2.3	9.3
(n = 22)	S.D	10.7	19.8	78.9	4.7	1.6	8.7
AD	Av	65.4	17.4*	238.6	31.8	1.8	8.4
(n = 21)	S.D	13.1	10.4	38.7	4.0	0.9	6.4
Early-onset AD	Av	49.6	10.3	221.6	33.8	1.2	3.9
(n = 7)	S.D	8.1	5.4	16.5	4.8	0.3	3.3
Late-onset AD	Av	73.3	20.9**	247.2	30.8	2.1	10.7**
(n = 14)	S.D	5.6	10.7	44.1	3.3	1.0	6.5
PD	Av	68.7	18.8**	263.9	31.6	3.3*	14.5**
(n = 20)	S.D	5.8	6.9	112.9	3.6	2.1	7.6

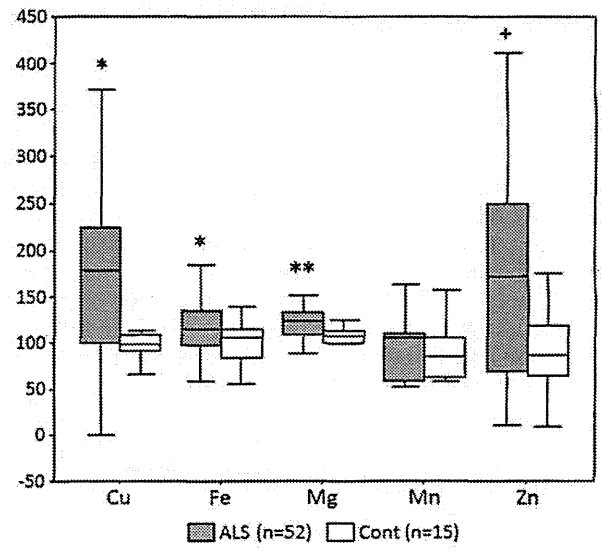

Fig. 1. The levels of the biological metals in the CSF of patients with ALS. The levels of Cu, Fe, Mg, Mn, and Zn in the CSF in patients and controls are shown in the box-and whisker type figure using SPSS. The levels of Mg (** significant difference: $p<0.01$), Fe, Cu (* $P<0.05$) and Zn (+ $p<0.10$), were higher in ALS patients than in controls.

In AD patients, we found significantly increased levels of Cu in the CSF ($p<0.05$). Then, we classified the AD patients according to the clinical subtype; early-onset AD (Alzheimer's disease with the onset under 65 years) ($n=7$) and late-onset AD (senile dementia of Alzheimer type (SDAT), onset at 65 and over 65 years) ($n=14$) (Table 1). The levels of Cu and Zn in the CSF were significantly higher in the patients with late-onset AD than in the controls. Correlation between the levels of Cu and Zn in the CSF was clearly recognized in patients with AD ($\sigma=0.812$) as well as in the controls ($\sigma=0.725$), but not in patients with ALS or PD. Although the ages of AD patients were significantly higher than those of the controls, the level of each metal did not correlate with the ages of the controls and AD patients. No other significant correlations could be observed between the levels of metals in the CSF and clinical manifestations such as MMSE, and serum Cu and Zn levels in this study. We show the levels of the biological metals in the CSF only in late-onset AD in Fig. 2.

In PD patients, we found significantly increased levels of Cu and Zn in particular ($p<0.01$), and Mn ($p<0.05$) in CSF (Table 1). We show the levels of the biological metals in the CSF in PD in Fig. 3.

In addition, to clarify the pathognomonic features, we performed a multiple comparison using Tukey's HSD test. The level of Mg in ALS was significantly higher than those in AD and PD ($p<0.01$). The level of Mn in PD was significantly higher than those in ALS and AD ($p<0.01$) (Fig. 4).

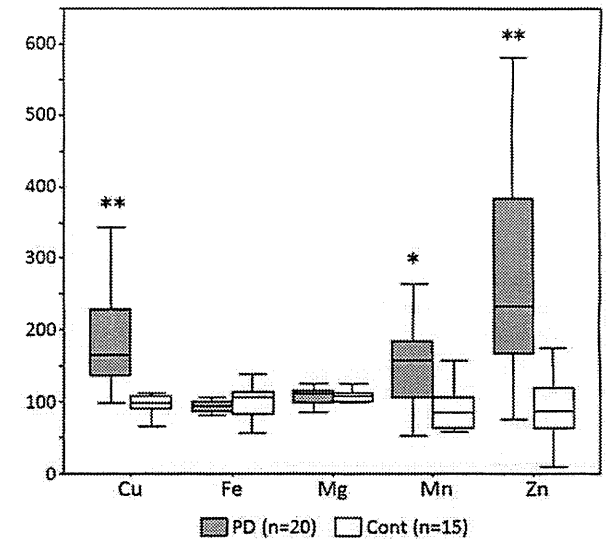

Fig. 3. The levels of biological metals in the CSF of patients with PD. The average levels of Cu, Fe, Mg, Mn, and Zn in the CSF in patients and controls are shown in the box-and whisker type figure using SPSS. The average levels of Mg, Fe, Cu, Zn, and Mn in the CSF in controls are shown to be set at 100 (%) in the figure. The levels of Cu and Zn (** $p<0.01$, respectively) and Mn (* $P<0.05$) in CSF were higher in PD patients than in controls.

4. Discussion

We measured the levels of some important metals (Cu, Fe, Mg, Mn, and Zn) in the CSF of patients with neurodegenerative diseases (AD, PD and ALS). We were able to find some pathognomonic patterns in the levels of the biological metals in the neurodegenerative diseases. Several remarkable studies on metals in the CSF of patients with neurodegenerative diseases have been published and we discuss some important metals for each disease.

In ALS, Kanias and Kapaki reported that the levels of Cu and Zn in CSF were higher in patients with ALS (age >40) than in older controls (age >40) as determined by atomic absorption spectrophotometry [13]. This is compatible with our finding. In particular, Cu and Zn are considered to play pivotal roles in the onset and/or progression of ALS. Studies on the spinal cord of G93A SOD-1 transgenic mice revealed high levels of Cu and labile Zn [14,15]. In this study, intriguingly, 5 patients showed very high levels of Cu and Zn before their critical deterioration. A researcher had observed that some patients with ALS showed transiently high levels of Zn in the urine during the course of the disease (personal communication). The mechanism remains to be elucidated and it remains to be clarified whether these phenomena are a harbinger or a result. In our study the levels of Mg were also significantly elevated ($P<0.01$) and the levels of Fe are also increased than those in the controls ($p<0.10$). Glutamate excitotoxity is suspected to cause motor neuron damage [16] and Mg ions inhibit the opening of NMDA receptors [17]. Taken together, the findings

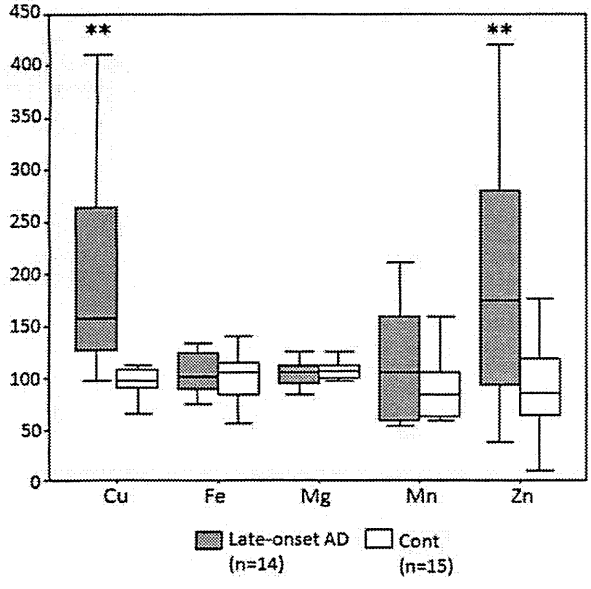

Fig. 2. The levels of biological metals in the CSF of patients with late-onset AD. The average levels of Cu, Fe, Mg, Mn, and Zn in the CSF in patients and controls are shown in the box-and whisker type figure using SPSS. The average levels of Mg, Fe, Cu, Zn, and Mn in the CSF in controls are shown to be set at 100 (%) in the figure. The levels of Cu and Zn (** $p<0.01$, respectively) in CSF were higher in late-onset AD than in controls.

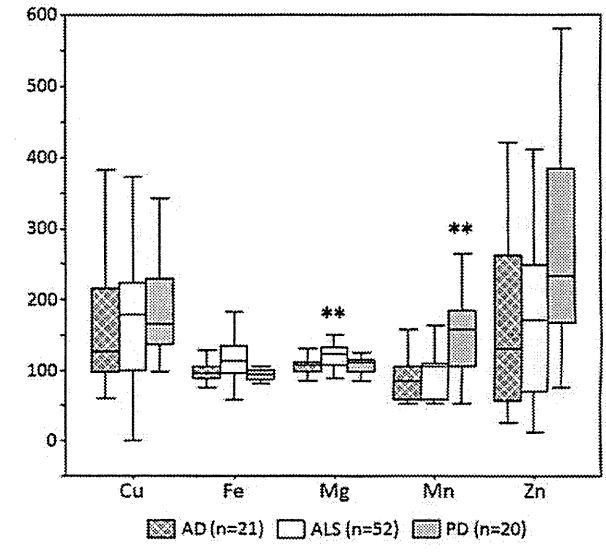

Fig. 4. The levels of the biological metals in the CSF among patients with ALS, AD and PD. The level of Mg in ALS patients was significantly higher than those in AD and PD patients (** $p<0.01$), and the levels of Mn were significantly higher than those in ALS and AD patients (** $p<0.01$) according to Tukey's HSD test.

suggest that multiple metals complexly contribute to the onset and/or progression of ALS.

We selected the patients with typical AD features using imaging studies, because the levels of Mg and Ca were reported to be increased in the CSF in patients with Levy body disease (LBD) than in those with AD [18]. Our study showed that the levels of Cu and Zn in CSF markedly higher in patients with late-onset AD. As similarly observed in ALS [13], markedly higher levels of Cu and Zn were also observed in late-onset AD patients in our study. However, no association of the levels of metals with age was found in both controls and patients with AD. A recent study showed that the serum copper level is associated with the MMSE score worsening in patients with AD [19]. Zn level was also reported to be increased in the human AD-affected cortex [20]. However, we found no association among the level of Cu in the CSF, the level of Cu in the serum, and the MMSE score in this study. A positive correlation between Cu and Zn levels in CSF was found in controls and patients with AD, although it is generally considered that there is a negative correlation between Cu and Zn levels in serum. However, the positive correlation between Cu and Zn levels in CSF in patients with AD was not observed in patients with ALS and PD. The mechanism underlying the correlation is unclear but some other pathognomonic factors may affect the levels of Cu or/and Zn in patients with ALS and PD. A study on Japanese American men suggested that Zn and Cu modulate Aβ-42 levels in CSF [21]. Therefore, both Cu and Zn are considered to be the main metals that are strongly associated with the onset and/or progression of AD, particularly late-onset AD.

In PD, our study showed that the levels of Cu and Zn in CSF were significantly ($p<0.01$) higher and the level of Mn was also higher ($p<0.05$) than those in the controls. Mn intoxication has been well known to cause parkinsonism. A survey suggested that chronic occupational exposure to Mn or Cu is associated with PD [22]. Low-level Mg intake over generations was shown to cause the degeneration of the substantial nigra in rats [23]. A study by ICP-AES showed lower Fe and Si levels in the CSF of 91 PD patients than in 18 controls in Italy and the levels of Mg concentration decreased in the CSF with the duration and severity of the disease [24]. The lower level of Fe and the decrease in the levels of Mg with time were not observed in our study. The reason is still unknown.

There are other studies on metals in the CSF of AD, PD and ALS patients. The important points are the methods of measurement of metals and the diagnosis of the diseases. ICP-MS is more sensitive and accurate than the conventional colorimetery and atomic absorption spectrophotometry methods for the simultaneous measurement of several biological metals such as Cu, Fe, Mg, Mn, and Zn [4,9]. We are able to accurately diagnose AD and PD by neuroimaging techniques [5–7]. However, there are some limitations in our study. The numbers of controls, and AD and PD patients were relatively small, and controls were significantly younger than the patients with ALS, AD, and PD ($p<0.01$). However, the levels of the metals in the CSF did not correlate with age. There may be several pathological factors that affect the levels of the metals in the CSF such as environmental factors including diet, drugs, life styles, the time of examination, and possibly races. We should examine the changes in the levels of metals in the CSF during the course of the diseases, particularly ALS. The levels of metals in the CSF only indicate the levels of metabolites similar to those in urine. We should examine the changes in the levels of metals and metal-transporting proteins in the causative parts for each disease to clarify the roles of metals in the brain and the spinal cord in the future.

Taken together, Cu and Zn are considered to play important roles in ALS, AD, and PD. Multiple metals seem to complexly contribute to the development of ALS and a surge of Cu or Zn level may be a harbinger of critical deterioration in ALS. The increased level of Cu and Zn in the CSF were prominent in the late-onset AD. The increased level of Mg in ALS and that of Mn in PD may be pathognomonic features. Cu and Zn may not be essential for the pathogenesis of neurodegenerative diseases but they probably promote the progression of the diseases through oxidative stress and conformational change of pivotal proteins. Cu-chelating agents [14], Zn-chelating agents [15], and, moreover, metallothioneins, which maintain Zn and Cu homeostasis [25,26], can be new candidates for the treatment of neurodegenerative diseases, based on the findings.

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References

[1] Crichton RR, Ward RJ. Metal-based neurodegeneration. England: John Wiley& Sons; 2006.
[2] Harris ED. Basic and clinical aspects of copper. Crit Rev Clin Lab Sci 2003;40: 547–86.
[3] Cuajungco MP, Lees GJ. Zinc metabolism in the brain: relevance to human neurodegenerative disorders. Neurobio Dis 1997;4:137–69.
[4] Hozumi I, Koumura A, Kimura A, Hasegawa T, Honda A, Hayashi Y, Hashimoto K, Yamada M, Sakurai T, Tanaka Y, Satoh M, Inuzuka T. High levels of copper, zinc, iron, and magnesium, but not calcium in the cerebrospinal fluid of patients with Fahr's disease. Case Rept Neurol 2010;2:46–51.
[5] Hirata Y, Matsuda H, Nemoto K, Ohnishi T, Hirao K, Yamashita F, Asada T, Iwabuchi S, Samejima H. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. Neurosci Lett 2005;382:269–74.
[6] Matsuda H, Mizumura S, Nagao T, Ota T, Iizuka T, Nemoto K, Takemura N, Arai H, Homma A. Automated discrimination between very early Alzheimer disease and controls using an easy Z-score imaging system for multicenter brain perfusion single-photon emission tomography. Am J Neuroradiol 2007;28:731–6.
[7] Orimo S, Ozawa E, Nakade S, Sugimoto T, Mizusawa H. 123I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;67:189–94.
[8] Turner BJ, Talbot K. Transgenics, toxicity and therapeutics in rodent models of mutant SOD1-mediated familial ALS. Prog Neurobiol 2009;85:94–134.
[9] Gellein K, Roos PM, Evje L, Vesterberg O, Flaten TP, Nordberg M, Syversen T. Separation of proteins including metallothionein in cerebrospinal fluid by size exclusion HPLC and determination of trace elements by HR-ICP-MS. Brain Res 2007;1174:136–42.
[10] Brooks BR, Miller RG, Swash M, Musat TL. World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Mot Neuron Disord 2000;1:1293–9.
[11] 4th ed. DSM-IV. American Psychiatry Association, Washington D.C., 1994.
[12] Hughes AJ, Daniel SE, Kliford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease; a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatr 1992;55:181–4.
[13] Kanias D, Kapaki E. Trace elements, age, and sex in amyotrophic lateral sclerosis disease. Biol Trace Elem Res 1997;56:187–201.
[14] Tokuda E, Ono S, Ishige K, Watanabe S, Okawa E, Ito Y, Suzuki T. Ammonium tetrathiomolybdate delays onset, prolongs survivals, and slows progression of disease in a mouse model for amyotrophic lateral sclerosis. Exper Neurol 2008;213:122–8.
[15] Kim J, Kim T-Y, Hwang JJ, Lee Y-Y, Shin J-H, Gwag B-J, Koh J-Y. Accumulation of labile zinc in neurons and astrocytes in the spinal cords of G93A SOD-1 transgenic mice. Neurobiol Dis 2009;34:221–9.
[16] Shaw PJ. Motor neuron disease. Br Med J 199;318:1118-1121.
[17] Mayer ML, Westbrook GL, Guthrie PB. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurons. Nature 1984;309:261–3.
[18] Bostroem F, Hassen O, Gerhardsson L, Lundh T, Minthon L, Stomrud E, Zetterberg H, Londos E. CSF Mg and Ca as diagnosis markers for dementia with Lewy bodies. Neurobiol Aging 2009;30:1265–71.
[19] Squitti R, Bressi F, Pasqualetti, Bonomini C, Ghidoni R, Binetti G, Gassetta F, et al. Longitudinal prognostic value of serum "free" copper in patients with Alzheimer disease. Neurology 2009;72:50–5.
[20] Religa D, Strozyk D, Cherny RA, Volitakis I, Haroutunian V, Winblad B, Naslund J, Bush AI. Elevated cortical zinc in Alzheimer disease. Neurology 2006;67:69–75.
[21] Strozyk D, Launer LJ, Adlard PA, Cherny RA, Tsatsanis A, Volitakis I, Blennow K, Petrovitch H, White LR, Bush AI. Zinc and copper modulate Alzheimer Aβ levels in human cerebrospinal fluid. Neurobiol Aging 2009;30:1069–77.
[22] Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology 1999;20:239–47.
[23] Oyanagi K, Kawakami E, Kikuchi-Horie K, Ohara K, Ogata K, Takahama S, Wada M, Kihira T, Yasui M. Magnesium deficiency over generations in rats with special

references to the pathogenesis of the parkinsonism–dementia complex and amyotrophic lateral sclerosis of Guam. Neuropathol 2006;26:115–28.
[24] Bocca B, Alimonti A, Senofonte O, Pino A, Violante N, Petrucci F, Sancesario G, Forte G. Metal changes in CSF and peripheral compartments of parkinsonian patients. J Neurol Sci 2006;248:23–30.
[25] Hozumi I, Asanuma M, Yamada M, Uchida Y. Metallothioneins and neurodegenerative diseases. J Health Science 2004;50:323–31.
[26] Miyayama T, Suzuki KT, Ogra Y. Copper accumulation and compartmentalization in mouse fibroblast lacking metallothionein and copper chaperone, Atox1. Toxicol Appl Pharm 2009;237:205–13.

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ORIGINAL ARTICLE

High frequency of calcification in basal ganglia on brain computed tomography images in Japanese older adults

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Aim: To investigate the frequency of calcification in the basal ganglia and the dentate nuclei in the cerebellum, and compare the difference in age and area, we examined the brain computed tomography (CT) images of all patients in two representative university hospitals in Japan.

Methods: We examined the brain CT images of 2526 patients in Gifu University Hospital (UH) and 2573 patients in Niigata UH. These patients were examined in these hospitals from October 2009 to September 2010.

Results: Punctate calcification of the basal ganglia was observed in 435 of 2526 patients (17.2%) in Gifu UH and 530 of 2573 patients (20.6%) in Niigata UH. The frequency of calcification increased with age. Patchy calcification of the basal ganglia was observed in 32 (1.3%) and 50 patients (1.9%) in Gifu UH and Niigata UH, respectively. Among patients aged over 65 years, 24 (2.1%) and 34 (3.1%) patients showed patchy calcification in Gifu UH and Niigata UH, respectively. Calcification of the cerebellar dentate nuclei was detected in just seven and four patients in Gifu UH and Niigata UH, respectively.

Conclusion: Compared with previous reports, the frequency of calcification of the basal ganglia in this study markedly increased. This might be because of the increased number of older adults and the increased sensitivity of CT. **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: basal ganglia, calcification, cerebellar dentate nucleus, diffuse neurofibrillary tangles with calcification, Fahr's disease.

Introduction

Calcification of the basal ganglia was first reported in 1850 by Delacour.[1] Calcification in the brain usually occurs bilaterally, and is commonly detected in the basal ganglia, dentate nucleus, thalamus, and centrum semiovale.[2] Pathological calcification in these areas has been detected on computed tomography (CT) images in various disorders, such as endocrinological, genetic, infectious, metabolic, and neoplastic and idiopathic disorders (so-called Fahr's disease).[3]

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CT is considered a more sensitive technique than magnetic resonance imaging system (MRI) for the detection of calcification. Previous studies, mainly in the 1980s, showed that the frequency of calcification in the basal ganglia detected by CT is in the range of 0.3–10%.[4–8] Nowadays, resolution of CT has been well developed and the numbers of older adults are more than before. Therefore, the frequency of calcification on the CT image should be re-evaluated at each age group.

Recently, more patients with diffuse neurofibrillary tangles with calcification (DNTC) have been detected in autopsy cases in Japan, and also found in the USA.[9–11] They showed various degrees of calcification of the basal ganglia from being punctate to patchy on CT images. The post-mortem examinations of such patients showed that diffuse neurofibrillary tangles were widespread in the cerebral cortex, and that calcification of the small vessels and capillaries was widespread in the

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