Journal of the Neurological Sciences 405 (2019) 116429

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

GDF-15, a mitochondrial disease biomarker, is associated with the severity of multiple sclerosis

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ARTICLE INFO

Keywords:
Mitochondria disorders
Multiple sclerosis
Neuromyelitis optica spectrum disorders
Biomarker
GDF-15
FGF-21

ABSTRACT

GDF-15, a member of the transforming growth factor beta superfamily, regulates inflammatory and apoptotic pathways in various diseases, such as heart failure, kidney dysfunction, and cancer. We aimed to clarify potentially confounding variables affecting GDF-15 and demonstrate its utility as a mitochondrial biomarker using serum samples from 15 patients with mitochondrial diseases (MD), 15 patients with limbic encephalitis (LE), 10 patients with multiple sclerosis/neuromyelitis optica spectrum disorders (MS/NMOSD), and 19 patients with amyotrophic lateral sclerosis (ALS). GDF-15 and FGF-21 were significantly elevated in MD. GDF-15 and FGF-21 showed a good correlation in MD but not in LE, MS, and ALS. GDF-15 was potentially influenced by age in LE, MS/NMOSD, and ALS but not in MD. FGF-21 was not correlated with age in MS/NMOSD, ALS, LE, and MD. GDF-15 was not correlated with clinical features in LE or BMI or body weight in ALS. GDF-15 positively correlated with the Expanded Disability Status Scale (EDSS) in MS/NMOSD, while EDSS showed no correlation with age. In conclusion, the results revealed that GDF-15 may be influenced by EDSS in MS/NMOPSD and by age in LE, MS/NMOSD, and ALS but not in MD. Mitochondrial damage in MS/NMOSD is a potentially confounding variable affecting GDF-15.

1. Introduction

Mitochondrial diseases (MDs) are complex inherited diseases resulting from failures in mitochondrial function and are typically diagnosed by various clinical investigations including muscle biopsy. Diagnosis of these diseases without invasive and painful investigations would be useful, particularly for pediatric patients.

Suomalainen et al. reported fibroblast growth factor-21 (FGF-21) as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies with 92.3% sensitivity and 91.7% specificity [1]. Yatsuga et al. reported growth differentiation factor-15 (GDF-15) as a novel biomarker of MD with 97.9% sensitivity and 95.2% specificity [2]. GDF-15 was first identified in microarray analysis of 2SD hybrid cells harboring an MD mutation and treated with lactate [3,4]. GDF-15 is known to be increased in disease states such as heart failure and kidney dysfunction [3–5]. Thus, clarifying the potentially confounding variables affecting GDF-15 measurement in neurological diseases is important for determining its importance as a mitochondrial biomarker.

2. Patients and methods

Serum samples were obtained from patients with MD, limbic encephalitis (LE), multiple sclerosis/neuromyelitis optica spectrum disorders (MS/NMOSD), and amyotrophic lateral sclerosis (ALS). The patient details are presented in Table 1. All patients with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-

Abbreviations: MD, mitochondrial disease; LE, limbic encephalitis; MS/NMOSD, multiple sclerosis/neuromyelitis optica spectrum disorders; ALS, amyotrophic lateral sclerosis; GDF-15, growth differentiation factor-15; FGF-21, fibroblast growth factor-21

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https://doi.org/10.1016/j.jns.2019.116429
Received 2 February 2019; Received in revised form 14 August 2019; Accepted 14 August 2019
Available online 22 August 2019
0022-510X/

Table 1
Average age of patients: MD (44 years), LE (47 years), MS/NMOSD (44 years), and ALS (57 years).

	Age	Sex	Diagnosis	Clinical feature	Gene (heteroplasmy%)	BMI	Diabetes	Lactate	Pyruvate	GDF-15	FGF-21	Other findings
1	24	M	MELAS	Weakness Epilepsy MR	m. 3243A > G(72)	14.9	–	19.6	0.61	2581.5	387	RRF SSV
2	25	M	MELAS	Weakness Epilepsy Psychosis	m. 3243A > G(79)	14.2	–	28.1	1.07	3795.3	1087.4	RRF
3	32	M	MELAS	Weakness Deafness	m. 3243A > G(ND)	17.3	+	16.5	0.77	1809.3	1255.4	RRF
4	32	F	MELAS	Weakness Epilepsy MR Deafness	m. 3243A > G(56)	16.7	–	20.3	0.73	1679.1	1193.3	RRF
5	33	F	MELAS	Weakness Deafness	m. 3243A > G(ND)	15.2	+	23.5	0.78	6863.6	1331.3	RRF SSV
6	39	M	MELAS	Hemiparasis Deafness Myoclonus	m. 3243A > G(ND)	17.7	+	36.8	1.49	1686.2	907.2	
7	50	F	MELAS	LOC Tremor	m. 3243A > G(ND)	21.7	+	56.9	2.25	2453.7	623.7	
8	51	M	MELAS	Epilepsy Aphesia Deafness	m. 3243A > G(> 30)	17.1	+	33	2.4	10,623.3	2313.3	
9	51	M	MELAS	Weakness Epilepsy Psychosis Deafness	m. 3243A > G(ND)	13.9	+	34.5	1.15	3447.4	1988.8	
10	26	F	MELA	Deafness WPW sundrome	m. 3243A > G(ND)	18.9	+	29.5	1.81	719.1	185.3	
11	41	M	MELA	Weakness Deafness	m. 3243A > G(87)	20.3	+	25.1	1.11	1694.5	242.7	RRF
12	59	F	MELA	Deafness Ataxia Atrophy Dementia	m. 3243A > G(ND)	14.5	+	12.6	0.8	842.3	463.5	
13	68	F	MELA	Deafness	m. 3243A > G(75)	20	+	13.2	0.62	2084.3	519.3	
14	55	F	CPEOp	Ptosis Weakness Diplopia	ND	28.1	–	19.2	0.8	1897.3	1171.5	RRF
15	76	M	CPEOp	Ptosis Diplopia	ND	22.7	+	14.7	0.68	2334.9	< 7	
16	28	F	aGluR LE	Psychosis		17.4	–	10.7	0.62	430.1	234.3	cPro/cCell 159/1
17	37	M	aGluR LE	Headache Fever		22.1	–	ND	ND	650	247.2	cPro/cCell 211/119
18	46	F	aGluR LE	Epilepsy		22	–	17.8	0.94	20.5	< 7	cPro/cCell 21/0
19	48	M	aGluR LE	Gait disturbance		23.1	–	8.2	0.88	498.4	227.8	cPro/cCell 52/10
20	48	F	aGluR LE	Epilepsy		19.5	+	5.6	0.33	363.1	195.9	cPro/cCell 30/1
21	64	F	aGluR LE	LOC		24.5	–	9.1	0.72	227.9	< 7	cPro/cCell 40/4
22	67	F	aGluR LE	Epilepsy		21.5	–	8.5	0.73	863.3	328.4	cPro/cCell 50/0
23	26	F	aNMDA LE	Headache		18.3	–	11	0.9	398.4	16	cPro/cCell 37/64
24	55	F	aNMDA LE	Epilepsy		18	–	ND	ND	2557.2	< 7	cPro/cCell 68/2
25	21	F	HUS encephalitis	LOC Fever Diarrhea		19	–	ND	ND	134.4	< 7	cPro/cCell 31/17
26	37	F	CNS lupus	Dementia Apraxia Dizziness		18.9	–	6.9	0.52	425.4	42.7	cPro/cCell 76/7
27	69	F	VZV encephalitis	LOC		19.4	–	ND	ND	1189.7	389.6	cPro/cCell 140/43
28	24	M	Tuberculosis	Headache		17.5	–	9.7	1.02	1667.2	681.5	cPro/cCell 43/29
29	59	M	paraneoplastic (SLC)	Gait disturbance LOC		22.5	–	ND	ND	948.1	345	cPro/cCell 52/53
30	68	M	paraneoplastic (SLC)	Epilepsy LOC		22.5	–	ND	ND	1419.4	461.4	cPro/cCell 36/2
31	23	F	MS	Dysesthesia		23.7	–	ND	ND	279.1	78.3	
32	30	F	MS	Dysesthesia		16.4	–	ND	ND	274.4	< 7	
33	31	F	MS	Muscle weakness		21.1	–	9	0.6	2970.8	1914.3	
34	38	F	MS	Visual impairment		19.9	–	ND	ND	1342.4	773.2	
35	38	M	MS	Vision impairment		24	–	ND	ND	404.4	78.7	Hepatitis C
36	42	M	MS	Dysarthria		24.9	–	ND	ND	323.3	71.6	
37	47	M	MS	Muscle weakness		24.1	–	24.8	2.46	524.7	181.5	
38	55	F	MS	Dysesthesia, Weakness		26.8	–	ND	ND	1427.8	643	
39	57	F	MS	Dysesthesia		23.6	–	ND	ND	487.6	99.5	
40	68	M	MS	Dysesthesia		17	–	ND	ND	575.2	< 7	esophageal cancer
41	34	F	NMO	Vision impairment		27.2	–	12.6	1.27	133.3	< 7	AQP4(+), Cervical cancer
42	36	F	NMO	Muscle weakness		19.5	–	ND	ND	729.4	77.6	AQP4(+)
43	53	F	NMO	Dysesthesia		20.1	–	ND	ND	857	249	AQP4(+)
44	71	F	NMO	Vision impairment		28.6	–	ND	ND	1020.1	102.2	AQP4(+)
45	30	F	ALS	Dyspnea		13.9	–	9.3	0.67	191	< 7	
46	30	F	ALS	Dyspnea	SOD	19.2	–	ND	ND	210.6	< 7	
47	33	M	ALS	Muscle weakness	SOD	24.3	+	15.2	0.4	311.1	9731.3	Lactate/Pyruvate ratio > 20
48	42	M	ALS	Muscle weakness		20.9	–	4.2	0.4	394.4	70.4	
49	42	M	ALS	Muscle weakness		21	–	15.9	1.18	270.8	< 7	
50	48	M	ALS	Muscle weakness		20.9	–	ND	ND	608.3	11.5	
51	53	F	ALS	Dyspnea		13.3	–	ND	ND	655.3	226	
52	55	M	ALS	Dyspnea		14	–	11.3	0.54	737.4	124.7	esophageal cancer
53	60	F	ALS	Muscle weakness		12.6	–	17.1	1.42	435	41.9	
54	61	M	ALS	Balbar palsy		14.2	–	6.4	0.39	690	< 7	
55	66	M	ALS	Muscle weakness		22.8	–	5.3	0.47	854.4	85.9	
56	68	F	ALS	Muscle weakness		11.8	–	8.6	0.6	793.9	414.2	
57	72	F	ALS	Muscle weakness		20.3	–	11.9	0.45	613.7	79.3	
58	72	F	ALS	Balbar palsy		14.5	–	10.7	0.52	858.7	233.8	
59	73	M	ALS	Dyspnea		14.7	–	ND	ND	842	199.1	
60	73	F	ALS	Muscle weakness		18.8	–	18.9	1.56	891.9	< 7	
61	79	F	ALS	Balbar palsy		18.1	–	ND	ND	838.5	5635.2	AST and Ck elevation. Using NPPV
62	79	F	ALS	Balbar palsy		16.6	–	13.8	1.23	549.6	< 7	

(*continued on next page*)

Table 1 (*continued*)

	Age	Sex	Diagnosis	Clinical feature	Gene (heteroplasmy%)	BMI	Diabetes	Lactate	Pyruvate	GDF-15	FGF-21	Other findings
63	84	F	ALS	Balbar palsy		23.5	–	7.2	0.39	1298.2	541.4	

MR, mental retardation; DM, diabetes mellitus; RRF, ragged red fibers by modified Gomori trichrome staining in muscle biopsy; ND, not done; SSV, strongly SDH-reactive blood vessels by SDH staining in muscle biopsy; CCO, cytochrome *c* oxidase staining; CK, serum creatine kinase (normal range, 63–257 U/L; Lac/Pyru, lactate/pyruvate, normal range, 3.7–16.3 mg/dL/0.3–0.9 mg/dL); CSF pro, protein levels in cerebrospinal fluid (normal range, 10–40 mg/dL); CSF cell, number of cells in cerebrospinal fluid (normal range, 0–5/mm^3); EDSS, Expanded Disability Status Scale; Cre, serum creatinine (normal range, 0.61–1.04 mg/dL); eGFR, estimated glomerular filtration rate (normal range, > 90 mL/min); male eGFR (mL/min/1.73 m^2) = 194 × Cr – 1.094 × Age – 0.287; female eGFR (mL/min/1.73 m^2) = 194 × Cr – 1.094 × Age – 0.287 × 0.739; SOD, superoxide dismutase; CPEOp, chronic progressive external ophthalmoplegia plus.

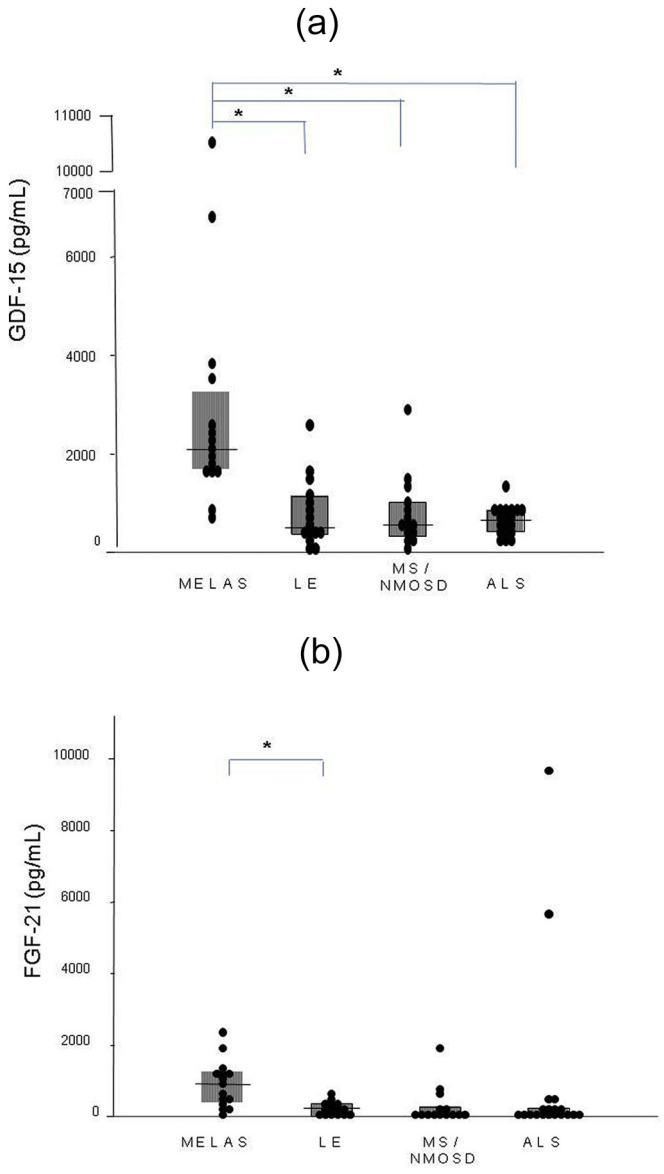

Fig. 1. GDF-15 (a) and FGF-21 (b) serum concentrations in neurological diseases.
Data are represented as the median ± the interquartile range using the Mann–Whitney U test between 2 groups. *$p < .005$.
Kruskal–Wallis analysis of variance for comparing multiple groups, followed by the Dunn multiple comparisons test. Kruskal–Wallis analysis of variance for comparison of multiple groups was used for age ($p = .04$), sex ($p = .54$), GDF-15 ($p < .001$), and FGF-21 ($p < .001$).

like episodes)/MELA (mitochondrial encephalopathy and lactic acidosis) carried the m.3243A > G mutation in their mitochondrial DNA. Chronic progressive external ophthalmoplegia plus (CPEOp) was diagnosed based on clinical symptoms and ragged red fibers in the muscle biopsy. LE was also diagnosed clinically. Seven patients with LE were positive for anti-GluR antibody, two possessed the anti-NMDA receptor antibody, and two had lung cancer. Other causes of LE were hemolytic uremic syndrome (HUS), CNS lupus, tuberculosis, and herpes zoster. MS was diagnosed by the 2017 McDonald diagnostic criteria [6]. All patients with NMOSD were positive for the anti-aquaporin-4 antibody. The serum GDF value of patients with MS/NMOSD was determined at the time of relapse or onset of the disease. Two patients with MS had colon and esophageal cancer, and one patient with NMOSD had cervical cancer. Patients with ALS fulfilled the Awaji criteria [7], and two patients carried the superoxide dismutase (SOD) mutation.

Enzyme-linked immunosorbent assay (ELISA) for evaluating GDF-15 (R&D Systems, Minneapolis, MN, USA) and FGF-21 (BioVendor, Brno, Czech Republic) levels in the patient sera was performed at Kurume University [2]. Pearson's correlation coefficient and Wilcoxon's rank sum test were used for statistical analysis. The Mann–Whitney *U* test was also used to compare GDF-15 and FGF21 levels between 2 groups, and the Kruskal–Wallis test or one-way analysis of variance for comparing multiple groups, followed by Dunn's multiple comparisons test [5].

All patients received adequate information concerning this study according to the guidelines of the Declaration of Helsinki (approval No. H26–093 by the Ethics Committee of the University of Tsukuba Hospital and No. #141 & #273 by the Ethics Committee of Kurume University) and provided informed consent.

2.1. Data availability

Anonymized data will be shared upon request from any qualified investigator for the purpose of replicating the procedures and results.

3. Results

The median levels of GDF-15 and FGF-21 in patients with MD were 2084.3 and 765.5 pg/mL, respectively. The median levels of GDF-15 and FGF-21 in patients with LE were 498.4 and 211.9 pg/mL, respectively, and those in patients with MS/NMOSD were 550.0 and 89.1 pg/mL, respectively. The levels of GDF-15 and FGF-21 in patients with ALS were 655.3 and 85.9 pg/mL, respectively. GDF-15 and FGF-21 were significantly elevated in patients with MD (Table 1). GDF-15 showed a significant difference between MD and LE (Mann–Whitney *U* test, $p < .05$), MS/NMOSD ($p < .05$), and ALS ($p < .05$). There was a good correlation between GDF-15 and FGF-21 levels in MD (Pearson correlation coefficient $r = 0.71$, $p = .002$, Supplementary Fig. 1), but not in LE ($r = 0.42$, $p = .12$), MS/NMOSD ($r = 0.07$, $p = .82$), and ALS ($r = 0.17$, $p = .48$). In MD, the correlation between GDF-15 and lactic acid; GDF-15 and pyruvate; FGF-21 and lactate; and FGF-21 and pyruvate was not significant (Supplementary Fig. 2).

There was no correlation between GDF-15/FGF-21 and clinical features such as daily level of activity (with or without aftereffects, Wilcoxon rank sum test; $p > .10/p > .05$), number of cells in the cerebrospinal fluid (CSF) ($r = 0.05$, $p = .96/r = 0.21$, $p = .43$), and

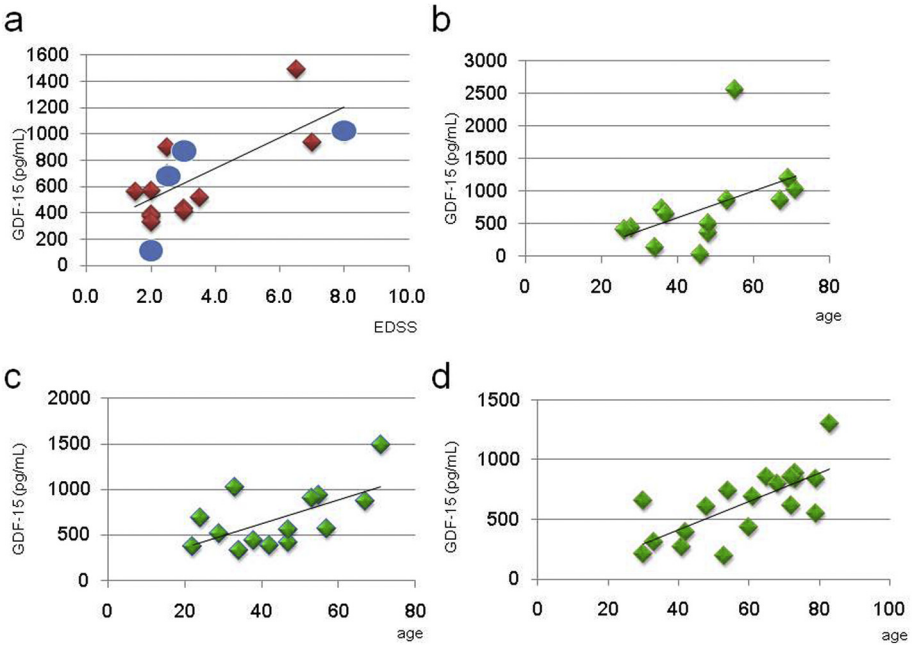

Fig. 2. a. EDSS and GDF-15 levels in MS (diamond)/NMOSD (circle).
$y = 115.49\times + 277.69$, $R^2 = 0.54$, $r = 0.74$ ($p = .0001$).
b. Age and GDF-15 levels in MS/NMOSD, $r = 0.60$ ($y = 12.986\times + 103.6$, $R^2 = 0.36$).
c. Age and GDF-15 levels in LE, $r = 0.23$ ($y = 20.478\times - 226.52$, $R^2 = 0.23$).
d. Age and GDF-15 levels in ALS, $r = 0.72$ ($y = 11.764\times - 57.054$, $R^2 = 0.514$).

brain magnetic resonance spectroscopy (MRI) findings (with or without MRI abnormality, Wilcoxon rank sum test; $p > .05$/p > .05) in LE.

No GDF-15 elevation was found in two patients with MS and one patient with NMOSD with cancer. There was no correlation between GDF-15/FGF-21 and the protein concentration of CSF in patients with LE ($r = 0.25$, $p = .80$/$r = 0.12$, $p = .64$).

GDF-15 showed a positive correlation with the Expanded Disability Status Scale (EDSS) in patients with MS/NMOSD ($r = 0.74$, $p < .0001$, Fig. 1). There was no correlation between EDSS and age in MS/NMOSD ($r = 0.23$, $p = .22$) or between EDSS and FGF-21 in MS/NMOSD ($r = -0.08$, $p = .67$).

Although two patients with ALS showed high FGF-21 levels, no correlation with severity and phenotypes was observed. GDF-15 was potentially influenced by age in MS ($r = 0.60$, $p = .002$, Fig. 2b) and ALS ($r = 0.72$, $p < .0001$, Fig. 2c), but not in MD ($r = 0.22$, $p = .40$) and LE ($r = 0.23$, $p = .007$, Fig. 2a). FGF-21 levels were not correlated with age in MS ($r = -0.25$, $p = .38$), ALS ($r = -0.15$, $p = .65$), LE ($r = -0.02$, $p = .93$), and MD ($r = 0.20$, $p = .41$). There was no correlation between GDF-15 and body mass index ($r = 0.01$, $p = .96$) or body weight ($r = -0.20$, p = .41) in patients with ALS.

4. Discussion

In this study, we found that GDF-15 outperforms FGF-21 as an indicator of MD, as previously reported [2,8–10]. Serum GDF-15 accurately distinguishes patients with MD from those with LE, MS/NMOSD, and ALS.

Mitochondrial dysfunction has been implicated in the pathophysiology of MS [11–13] and experimental autoimmune encephalomyelitis [11]. Damaged mitochondria contribute to axonal damage and neuronal loss in MS and NMOSD [11–13]. Mitochondrial DNA mutations have been shown to underlie neuronal mitochondrial dysfunction in MS [11–13]. Further evidence in which the Leber's hereditary optic neuropathy, one of the subtypes of MD, showed demyelination suggested a relationship between mitochondrial dysfunction and MS. EDSS is reported to correlate with the severity of white matter lesions in MS. Because GDF-15 is well correlated with EDSS (Fig. 2), GDF-15 is thought to reflect mitochondrial dysfunction in white matter lesions in MS. Additional disease-specific markers of MS are still needed, and thus studies are required to explore biomarkers related to MS progression and prediction. Although this study included a small number of samples, the results suggest that GDF-15 is a useful marker of MS progression. Measurement of GDF-15 by blood sampling is inexpensive compared to other methods such as frequent MRI imaging and genetic testing. However, for clinical application, it is important to accumulate data on the relapse and stable periods because the clinical features of MS are diverse. Measurement of GDF-15 in the CSF is also necessary to evaluate the severity of MS.

GDF-15 concentrations have been shown to increase with aging [14,15], and these changes are explained only partially by cardiovascular risk factors, indicators of neurohumoral activation and inflammation, and renal function, suggesting that GDF-15 reflects cardiovascular and other biological processes that are closely related to longevity [3,4]. Doerstling et al. showed that GDF-15 increased with age in healthy participants [15]. The GDF-15 value in adults is more useful as a biomarker for mitochondrial disease if age correction is performed.

In this study, we demonstrated that EDSS of MS/NMOSD and age are confounding factors affecting GDF-15. GDF-15 may be influenced by age in MS/NMOSD, LE, and ALS, but not in MD. FGF-21 levels were not correlated with age in MS/NMOSD, ALS, LE, and MD. The recent findings showing that GDF-15 is a marker for the diagnosis of MD and possibly mitochondrial dysfunction suggest that circulating GDF-15 levels at least partly reflect mitochondrial dysfunction in aging and age-related disorders. The significance of GDF-15 as a biomarker for mitochondrial function in aging and age-related disorders requires further examination.

5. Conclusion

We found that GDF-15 is a useful biomarker of MD. GDF-15 is potentially influenced by age in MS, LE, and ALS, but not in MD. There was no correlation with gender, co-morbidity, and co-medication in all patients examined. GDF-15 may also be influenced by disease severity in MS. However, this study was limited by the small number of cases. Additionally, serum was collected from patients, most of whom were Asian, who came to our hospital, indicating bias. Further studies of GDF-15 involving a greater number of cases and other degenerative diseases will help reveal the mechanism of its increased expression in MD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116429.

Funding

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) (grant number 16k07081 to A.I.) and AMED for Research on Intractable Diseases from the Ministry of Health, Labor, and Welfare of Japan (grant number 17ek0109088h0003 to Y.K. and A.I.).

Declaration of Competing Interest

Seitaro Nohara, MD, Fumiko Yamamoto, MD, PhD, Kumi Yanagiha, MD, Tetsuya Moriyama, MD, Naoki Tozaka, MD, Zenshi Miyake, MD, PhD, Takashi Hosaka, MD, Makoto Terada, MD, PhD, Tetsuto Yamaguchi, MD, Satoshi Aizawa, MD, Naomi Mamada, MD, PhD, Hiroshi Tsuji, MD, PhD, Yasushi Tomidokoro, MD, PhD, Kiyotaka Nakamagoe, MD, PhD, Kazuhiro Ishii, MD, PhD, Masahiko Watanabe, MD, PhD, and Akira Tamaoka, MD, PhD have no disclosures relevant to this manuscript.

Akiko Ishii, MD, PhD has received grants from the MEXT (no. 16k07081) and AMED (no. 17ek0109088h0003) for Research on Intractable Diseases from the Ministry of Health, Labor, and Welfare of Japan. Yasutoshi Koga, MD, PhD has received grants from AMED (no. 17ek0109088h0003) for Research on Intractable Diseases from the Ministry of Health, Labor, and Welfare of Japan. Shuichi Yatsuga MD, PhD has received grants from the MEXT (no. 25860891).

Acknowledgments

We would like to thank all patients in this study and Editage (www.editage.jp) for English language editing.

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