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ICAM-1, BDNF, and Neurobehavioral Profiles in Maple Syrup Urine Disease: Exploring Potential Biomarker Links

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Abstract

Background: Maple syrup urine disease (MSUD) is a rare inborn error of metabolism affecting branched-chain amino acid (BCAA) matabolism. Toxic accumulation of BCAAs disrupts critical neurodevelopmental processes and can induce neuroinflammatory and neuronal injury. Biomarkers such as Brain-Derived Neurotrophic Factor (BDNF) and Intercellular Adhesion Molecule-1 (ICAM-1) may reflect these neuroinflammatory and neurodevelopmental changes and could aid in improving disease monitoring, clinical care, and quality of life outcomes.

Methods: A case–control study was conducted on 42 Maple Syrup Urine Disease patients and 27 age- and sex-matched healthy controls at the Medical Genetics Department, Ain Shams University. Clinical, dietary, neurological data, amino acid profiling using Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS) were assessed and correlated with serum biomarkers, including BDNF and ICAM-1. Neurocognitive assessments (42/42 patients), behavioral assessments (38/42 patients), and brain Magnetic Resonance Imaging (MRI) (30/42 patients) were performed. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 12, with *p-value* < 0.05 considered statistically significant.

Results: In the studied patients, serum BDNF and ICAM-1 were markedly elevated compared with controls and were selectively associated with medullary MRI abnormalities and internalizing psychiatric symptoms, but not with metabolic control or neuromuscular findings.

Conclusion: BDNF and ICAM-1 are markedly elevated in Maple Syrup Urine Disease patients, which may provide insight into neuroinflammatory processes in MSUD and could be integrated into comprehensive patient monitoring strategies, potentially improving clinical outcomes and quality of life in affected patients.

Keywords: Maple syrup urine disease; BDNF; ICAM-1; Biomarkers; Neurodevelopment; Inborn errors of metabolism

1. Introduction

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive disorder caused by a deficiency of the branched-chain α-ketoacid dehydrogenase (BCKD) complex, impairing the oxidative decarboxylation of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine **(Strauss et al., 2020).** This defect leads to the accumulation of BCAAs and their α-ketoacids, with leucine being highly neurotoxic through the disruption of cerebral energy metabolism, inhibition of neurotransmitter synthesis and myelination, and competitive blockade of large neutral amino acid transport. Elevated metabolite levels also trigger mitochondrial dysfunction, oxidative stress, and neuroinflammation via microglial activation and pro-inflammatory cytokines, amplifying neuronal damage **(Amaral et al., 2022).** Globally, MSUD affects about 1 in 86,800 to 185,000 live births, but founder populations, such as Old Order Mennonites, show incidences up to 1:200 live births **(Puffenberger, 2003).**

MSUD can cause significant neurobehavioral impairment, including developmental delay, cognitive deficits, motor dysfunction, speech delay, and behavioral disturbances such as attention deficits, hyperactivity, and social withdrawal, largely due to recurrent metabolic crises and chronic neurotoxicity **(Xu et al., 2020).**

In MSUD, early pilot data and mechanistic reasoning position these two molecules as complementary serum biomarkers: altered BDNF levels—whether reduced or elevated—may reflect dysregulated neurotrophic signaling in MSUD, whereas elevated ICAM-1 may signal ongoing endothelial inflammation and cumulative blood–brain barrier (BBB) injury that predisposes to relapse or progressive damage **(Scaini et al., 2018).**

Brain-derived neurotrophic factor (BDNF) is a key neurotrophin that supports neuronal survival, synaptic plasticity, and neurogenesis **(Park et al., 2013),** while intercellular adhesion molecule-1 (ICAM-1), particularly its soluble form (sICAM-1), is an endothelial adhesion glycoprotein whose circulating levels index endothelial activation, leukocyte trafficking, and blood–brain barrier (BBB) disturbance **(Lawson et al., 2009).**

In MSUD, data regarding serum biomarkers remain limited. Serum BDNF levels have yielded conflicting results, with one study reporting reduced levels **(Scaini et al., 2018),** while another found no significant difference **(Castells et al., 2019).** In contrast, intercellular adhesion molecule-1 (ICAM-1) has been reported to be elevated in MSUD, with higher levels correlating with the number of metabolic crises (Scaini et al., 2018).

2. Materials and Methods

2.1 Study Design and Population

This case–control study was conducted at the Genetics Clinic, Medical Genetics Department, Ain Shams University, Cairo, Egypt. The study included 42 Egyptian patients with maple syrup urine disease (MSUD) and 27 age- and sex-matched healthy controls.

Inclusion Criteria:

Patients with MSUD including:

a) Biochemically confirmed patients with maple syrup urine disease (MSUD)
b) Age of the participants is 3 years or older
c) Both sexes are enrolled.

Exclusion criteria:

a) Patients with acute metabolic decompensation at the time of sampling
b) Patients with evidence of acute infection or inflammatory illness, and recent major surgery or trauma

Patients were recruited using a consecutive sampling strategy, whereby all eligible MSUD patients attending the clinic who met the inclusion criteria were enrolled sequentially until the target sample size was reached.

2.2 Clinical Assessment

A structured clinical history was obtained for all Maple Syrup Urine Disease patients, including developmental milestones assessed according to standardized developmental surveillance guidelines **(Zubler et al., 2022),** dietary intake, and history of metabolic decompensations. Dietary intake was evaluated using a 1-week food diary, with natural and total protein intake calculated in g/kg/day and compared with the target levels recommended by the Genetic Metabolic Dietitians International (GMDI) guidelines for the management of maple syrup urine disease **(Southeast Regional Genetics Network and Genetic Metabolic Dietitians International, 2024).** The history of metabolic decompensations included the frequency of episodes, with metabolic decompensation defined as acute neurological deterioration characterized by disturbed level of consciousness, seizures, documented brain edema, and/or the need for dialysis, consistent with published clinical descriptions of acute MSUD crises presenting with encephalopathy and neurological compromise **(Blackburn et al., 2017).** A comprehensive physical and neurological examination was performed for all patients.

2.3 Laboratory measurements

2.3.1 Amino Acid Analysis:

Patients' blood samples were obtained through finger pricks and placed on a Guthrie card (Whatman 903 filter paper, GE Healthcare, New Jersey). The blood spots were analyzed for amino acids profile by triple quadrupole tandem mass spectrometer (ACQUITY UPLC H-Class. Waters® Corporation, MA), with a positive electrospray ionization probe utilizing “Mass Chrom® amino acids and acyl carnitine Dried Blood kit” (Chromsystems Instruments and Chemicals GmbH, München, Germany), per the manufacturer's instructions. The data from the Multiple Reaction Monitoring (MRM) scan were analyzed using the Masslynx and Neolynx® applications (Waters® Corporation, MA). Leucine and isoleucine were quantified as a combined analyte (Xle), while valine was measured separately.

Metabolic control was interpreted according to established therapeutic target ranges for Maple Syrup Urine Disease management. Plasma leucine is maintained between 150–300 μmol/L, with isoleucine maintained at concentrations approximately comparable to leucine levels **(Southeast Regional Genetics Network and Genetic Metabolic Dietitians International, 2024).** Because leucine and isoleucine were measured together in this study, Xle values were used as a surrogate for leucine monitoring. An Xle concentration ≤450 μmol/L was considered compatible with acceptable metabolic control in clinically stable patients, reflecting the combined contribution of leucine and isoleucine within recommended therapeutic ranges **(Strauss et al., 2020).** Valine concentrations were interpreted according to recommended therapeutic targets (approximately 200–400 μmol/L) **(Strauss et al., 2020).**

2.3.2 Serum BDNF and ICAM-1 Measurement:

Fasting venous blood samples were collected in plain chemistry tubes. After clot formation, samples were centrifuged at 1000×g, and serum was separated and stored at –80 °C until analysis. Serum BDNF and ICAM-1 concentrations were measured using commercially available sandwich ELISA kits (BT LAB, China) according to the manufacturer's instructions. The ICAM-1 assay (Cat. No. E0212Hu) had a detection range of 20–6000 ng/L with a sensitivity of 9.56 ng/L and intra- and inter-assay coefficients of variation (CVs) of <8% and <10%, respectively. The BDNF assay (Cat. No. E1302Hu) had a measurement range of 0.05–10 ng/mL with a sensitivity of 0.01 ng/mL and intra- and inter-assay CVs of <10% and <12%, respectively. Optical density was measured at 450 nm using a Multiskan™ FC microplate reader, and concentrations were calculated from standard curves generated for each plate using regression analysis. All patients' samples were analyzed in duplicate, and the mean value was used for statistical analysis. Cases and controls were assayed under identical laboratory conditions using the same kit batch to minimize inter-assay variability.

2.4 Radiological Assessment

Brain Magnetic Resonance Imaging (MRI) was performed in 30 of 42 Maple Syrup Urine Disease patients using a 1.5 T Ingenia scanner. MRI abnormalities were categorized into seven regions: supratentorial white matter affection, encompassing the frontal, temporal, parietal, and occipital white matter, peri-trigonal region, centrum semiovale, and corona radiata; basal ganglia affection, including the internal capsule, corpus callosum, and other basal ganglia structures; midbrain affection; pontine affection; thalamic affection; medullary affection; and cerebellar affection **(Cheng et al., 2017).**

2.5 Neuropsychological and Behavioural Assessment

Cognitive assessment using the Stanford–Binet Intelligence Scales, Fifth Edition (SB-5), Arabic version, was performed in 21 of 42 patients who were cooperative and able to complete formal testing. IQ scores were categorized as follows: average (>90), below average (70–89), mild intellectual disability (55–69), moderate (40–54), severe (20–39), and profound (<20) **(Bain et al., 2005).**

Assessment using the Vineland Adaptive Behavior Scales, Third Edition (VABS-III), Arabic version, was performed in 21 of 42 patients who were unable to complete formal cognitive testing due to neurological impairment limiting cooperation. Scores were interpreted according to standardized norms **(Sparrow et al., 1989).**

Behavioral and emotional assessment using the Arabic version of the Child Behavior Checklist (CBCL 6–18) was performed in 38 of 42 patients. Permission to use the Arabic version was obtained from the Achenbach System of Empirically Based Assessment (ASEBA; License #2597-01-23-23). T-scores were interpreted as follows: <65 normal range, 66–70 borderline clinical range, and ≥71 clinically significant **(Achenbach et al., 2001).**

2.6 Ethical statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Research Ethics Committee (REC) of the Faculty of Medicine, Ain Shams University (approval number: FMASU MD82/2023), which operates under Federal Wide Assurance No. FWA 000017585 in accordance with the guidelines of the International Council on Harmonization (ICH) and the US Office for Human Research Protections. A written informed consent was obtained from the patients or their caregivers prior to enrollment.

2.7 Data Management and Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 27. IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. Statistical analyses were limited to standard descriptive, parametric, and nonparametric tests appropriate to data distribution, and no advanced modeling procedures were applied. All tests were two-tailed, and a $p\text{-}value < 0.05$ was considered statistically significant.

2.7.1 Descriptive Statistics

- Qualitative variables were summarized as frequencies and percentages.
- Quantitative variables were summarized as mean ± standard deviation (SD) for normally distributed data and median with interquartile range (IQR) for non-normally distributed data.

2.7.2 Analytical Statistics

- Comparison between categorical variables was performed using the Chi-square test.

- Comparison between two independent groups for quantitative variables was performed using the independent samples t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data.
- Comparisons among more than two groups were performed using one-way ANOVA or the Kruskal–Wallis test, as appropriate.
- Correlations between quantitative variables were assessed using Spearman's rank correlation coefficient.

3. Results

3.1 patient characteristics

A case-control study was carried out on 42 Egyptian patients diagnosed with Maple syrup urine disease from 39 families (6 siblings affected by the same disease were included in the study) following at Genetics Clinic, Medical Genetics Department, Ain shams university from November 2022 to April 2025 with 27 age-sex-matched controls for comparison regarding the serum levels of biomarkers (BDNF & ICAM-1).

Regarding sociodemographic characteristics of the studied patients were 50% males (21/42) & 50 % females (21/42) with a male-to-female ratio of 1:1. Their ages at study ranged between 3 and 23 years, with a median age of 8 (Interquartile IQR 6-11) years. As regards family history, parental consanguinity was observed in 90.5% (38/42) of the patients, and a family history of similarly affected siblings was detected in 57.1% (24/42) cases **(Table 1)** .

Table (1): Sociodemographic characterisation of the studied patients **(N=42).**

VARIABLES			N (%)
AGE AT STUDY (YEAR)	Median (IQR)	8(6 – 11)	
	Mean	8.89	
	Range	3 – 23	
GENDER	Male		21 (50.0%)
	Female		21 (50.0%)
FAMILY HISTORY OF MSUD	Negative		18 (42.9%)
	Positive		24 (57.1%)
CONSANGUINITY	Negative		4 (9.5%)
	Positive		38(90.5%)

* IQR: interquartile range; MSUD: maple syrup urine disease

Regarding the clinical phenotype of the studied patients, the classic MSUD phenotype was the most predominant 88% (37/42) of patients **(Figure 1)**

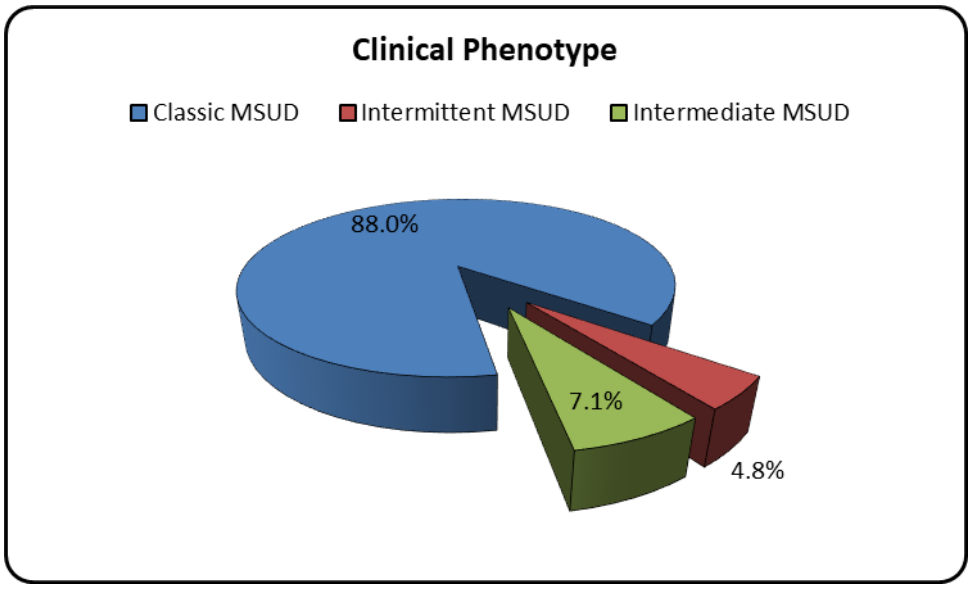


Figure 1: Clinical phenotype of the studied patients

3.2 Biomarkers and their correlations

Table 2 demonstrated that BDNF & ICAM-1 levels are ~14; **~12 times** higher in studied patients in comparison to the control group respectively, with median BDNF: 6.39 vs. median 0.46**;** median ICAM-1: 1848 vs. 152.3 in controls, respectively**.**

Table (2): Comparison between patients studied and control regarding biomarker levels (BDNF and ICAM-1).

Variables		Patients group	Control group	Test value	P-value	Sig.
		N. = 42	**N. = 27**			
BDNF (ng/ml)	Median (IQR)	6.39(2.22 – 10.45)	0.46(0.32-0.56)	-6.836≠	p < 0.001	S
	Mean ± SD	6.33 ± 4.23	0.44 ± 0.16			
	Range	0.5 – 12.8	0.18 – 0.84			
ICAM-1	Median	1848(677.92 – 2731)	152.3(105.9-	-6.713≠	p < 0.001	S

(IQR)		209.9)
Mean ± SD	1959.44 ± 1371.29	167.52 ± 76.06
Range	226.5 – 5224.5	61.71 – 335.6

BDNF: brain derived neurotrophic factor; ICAM-1: intracellular adhesion molecule 1; IQR: interquartile; SD: standard deviation; P-value > 0.05: Nonsignificant; P-value < 0.05: Significant; P-value < 0.01: Highly significant; ≠: Mann–Whitney U test.

Analysis of BDNF and ICAM-1 levels in the studied patients showed no statistically significant association with gender, protein intake, developmental delays, or amino acid levels (all $p > 0.05$) **(Table 3)**.

Table (3): Relation of BDNF and ICAM-1 with selected clinical & biochemical parameters among the patients studied (N=42).

Variable	BDNF Median (IQR), p-value	ICAM-1 Median (IQR), p-value
Gender	Male: 6.12 (2.22–9.98) Female:6.47(2.44–10.45), p=0.811	Male: 1878.5 (678–3428) Female: 1817.5 (1001–2585), p=0.792
Average intact protein	Below: 2.44 (0.79–10.63) Average: 8.03 (5.65–11.03) Above:4.38(1.93–8.98), p=0.092	Below: 1001 (266–2515) Average: 2360 (1781–2993) Above: 1347.1 (456–2320), p=0.108
Average total protein	Below: 2.44 (0.95–6.30) Average: 6.47 (2.22–10.63) Above:10.89 (9.59–12.2), p=0.168	Below: 1001 (368–2085) Average: 1817.5 (678–2993) Above: 2645.5 (2469–2823), p=0.390
Developmental delay	No: 7.73 (1.93–10.88) Yes: 6.21 (2.33–9.78), p=0.701	No: 2304.3 (455–2731) Yes: 1808.8 (837–2704), p=0.906
Leu. + Ile. Levels	Normal: 5.67 (1.3–10.45) Elevated:7.64(3.08–10.88), p=0.261	Normal: 1817.5 (455–2629) Elevated: 2143 (996–2823), p=0.565
Valine levels	Normal: 5.67 (1.25–11.03) Low:6.54(3.03–10.45), p=0.487	Adequate: 1698 (340–2823) Deficient: 2084.5 (1001–2731), p=0.370

BDNF: Brain-derived neurotrophic factor; ICAM-1: Intercellular adhesion molecule-1; IQR: Interquartile range; Leu.: leucine; Ile.: isoleucine; Val.: valine; NA: not applicable.
Normal leucine + isoleucine ≤450 µmol/L; normal valine ≥200 µmol/L.
P-value >0.05: Non-significant (NS).

An analysis examining the relationship between BDNF levels, ICAM-1 levels, and neuromuscular abnormalities found no statistically significant associations (all $p > 0.05$) (see Table 4).

Table (4): Relation of BDNF with neuromuscular findings among the studied patients (N=42).

Neuromuscular Finding	BDNF Median (IQR), p-value	ICAM-1 Median (IQR), p-value
Muscle tone	Normal: 3.08 (1.25–9.98) Abnormal: 7.25 (3.93–10.63), p=0.254	Normal: 1001 (368–2629) Abnormal: 2084.5 (1255–2731), p=0.311
DTR	Normal: 5.66 (1.93–10.45) Hyperreflexia: 6.64 (2.71–10.11), p=0.722	Normal: 1848 (455–2823) Hyperreflexia: 1898.8 (857–2658), p=0.722
Pathological reflexes	No: 5.98 (2.33–9.71) Yes: 7.64 (1.3–10.9), p=0.780	No: 1808.8 (832–2495) Yes: 2233 (456–2993), p=0.666
Muscle power	Good: 7.99 (2.44–11.0) NA: 6.53 (3.57–8.87) Weakness: 0.89 (0.81–2.47), p=0.059	Good: 2340 (985–3040) NA: 1907.5 (1146–2549) Weakness: 317.1 (246–935), p=0.050
CN affection	No: 6.5 (2.07–10.7)	No: 2083.5 (566–3016)

	Yes: 6.21 (3.21–7.25), p=0.658	Yes: 1739.3 (1037–2085), p=0.376
EPS	No: 6.12 (1.93–9.98)	No: 1800 (456–2731)
	Yes: 10.63 (8.03–11.1), p=0.136	Yes: 2584.5 (2515–2993), p=0.164
Contractures	No: 6.07 (2.48–10.7)	No: 2083.5 (720–2777)
	Yes: 6.42 (2.22–9.59), p=0.687	Yes: 1790.3 (678–2585), p=0.782
Ambulation	Ambulatory: 6.07 (1.61–10.7)	Ambulatory: 1790.3 (455–2777)
	Non-ambulatory: 6.78 (3.93–9.59), p=0.810	Non-ambulatory: 2041 (1255–2585), p=0.810
Cerebellar signs	Absent: 6.5 (2.22–10.9)	Absent: 1938 (678–2823)
	Present: 1.3 (0.95–3.21) NA: 8.03 (4–10.6), p=0.145	Present: 455.8 (368–1037) NA: 2360 (1503–2993), p=0.089

BDNF: Brain-derived neurotrophic factor; ICAM-1: Intercellular adhesion molecule-1; IQR: Interquartile range; DTR: Deep tendon reflexes; CN: Cranial nerves; EPS: Extrapyramidal signs; NA: Not applicable. P-value >0.05: Non-significant (NS).

Regarding MRI brain abnormalities among the available studied patients 71% (30/42). Abnormal MRI findings were documented in 66.7% (20/30) of participants with supratentorial affection 56.7% (17/30) was the most predominant abnormal findings followed by basal ganglia affection 33.3% (10/30), while a retro cerebellar cystic lesion (likely arachnoid cyst) and partial empty Sella with optic nerve sheath ectasia were the rarest 3.3% (1/30) for each. **(Table 5).**

Table (5): MRI brain abnormalities among the available patients studied (N=30).

			N (%)
MRI Brain	**Normal**		10 (33.3%)
	Abnormal	**Supratentorial affection***	17 (56.7%)
		Basal ganglia affection +	10 (33.3%)
		Midbrain affection	9 (30.0%)
		Pons affection	6(20%)
		Thalamus affection	6 (20.0%)
		Cerebellum affection	4 (13.0%)
		Medulla affection	3 (10.0%)
		Partial empty Sella & Optic nerve sheath ectasia	1 (3.3%)
		Retrocerebellar cystic lesion likely arachnoid cyst	1 (3.3%)

MRI: magnetic resonance imaging; &: and; * Supratentorial regions include frontal, temporal, parietal, occipital, peri-trigonal semiovale centrum, corona radiata; + basal ganglia comprise of internal capsule, corpus callosum, and other basal ganglia.

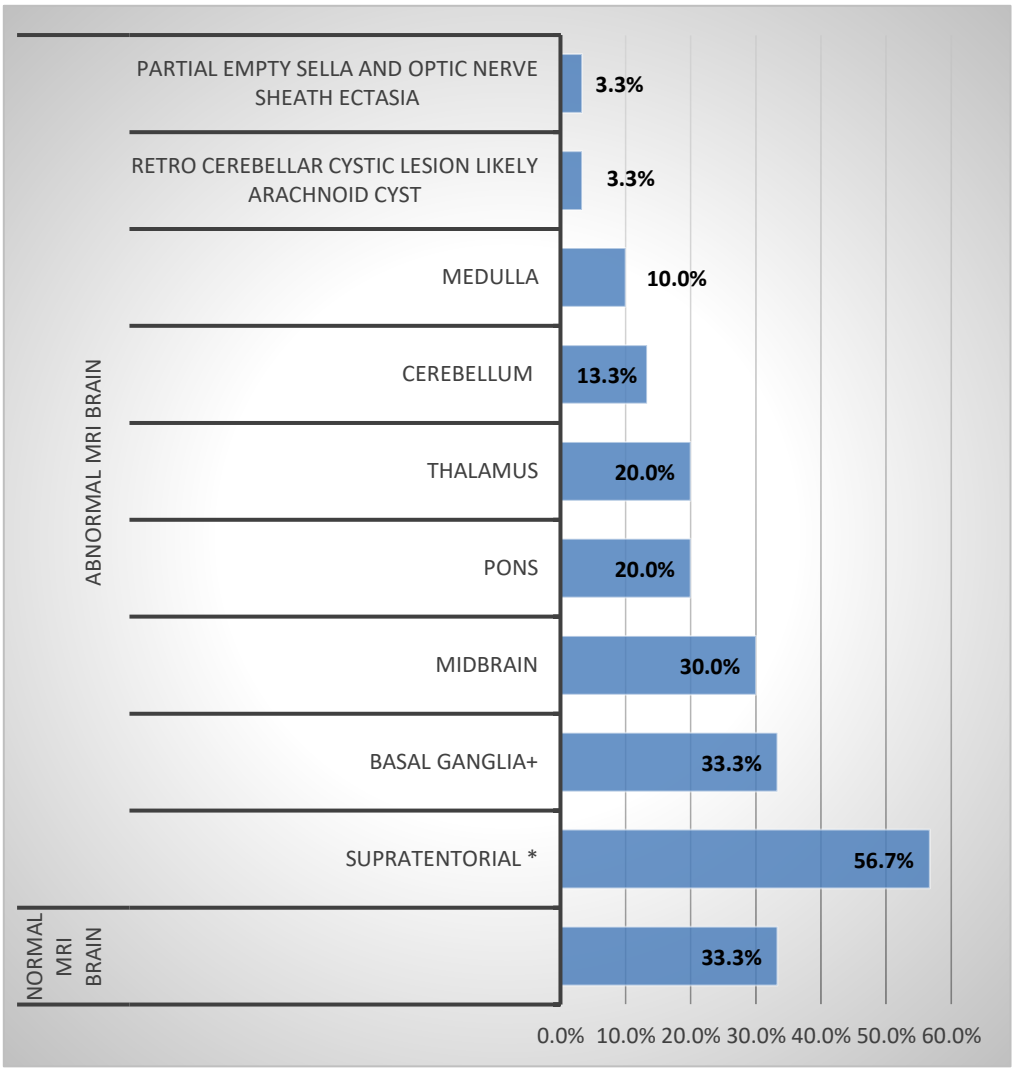


Figure (2): MRI brain abnormalities for the available studied patients.

Figure 2 illustrates that abnormal MRI findings were found in 66.7% (20/30) of participants, with supratentorial affection being the most predominant abnormal finding, followed by basal ganglia affection, 56.7% (17/30), and 33.3% (10/30), respectively.

Regarding the association between biomarker levels and radiological abnormalities, patients with medullary involvement on MRI demonstrated significantly higher BDNF levels compared to those without medullary changes (median: 11.03 vs. 6.30, p = 0.049) respectively. Similarly, ICAM-1 levels were markedly elevated in patients with abnormal medulla findings (median: 4356.5 vs. 1817.5, p = 0.049) respectively **(Table 6).**

Table (6): Relation between BDNF, ICAM-1 levels and MRI brain findings among the studied patients (N=30).

MRI Finding	BDNF Median (IQR)	P (Sig.)	ICAM-1 Median (IQR)	P (Sig.)
Overall MRI	Normal:7.87 (5.65–10.45) Abnormal:6.21(3.15–9.71)	0.428 (NS)	Normal:2304.25(1780.5–2629) Abnormal:1839.25(1016.6–2971)	0.628 (NS)
Supratentorial*	No:8.98 (5.65–10.45) Yes: 6.12 (3.21–8.76)	0.325 (NS)	No:2320(1780.5–2731) Yes:1800 (1036.95–2360)	0.325 (NS)
Midbrain	No: 6.54 (4–9.98) Yes: 5.67 (1.93–9.44)	0.572 (NS)	No:2084.5(1502.5–2629) Yes:1878.5(455.78–2360)	0.635 (NS)
Basal ganglia+	No: 7 (4.82–10.54)	0.202	No:2186.5(1641.5–2680)	0.291

	Yes: 4.8 (1.93–9.44)	(NS)	Yes:1476.38(455.78–2360)	(NS)
Cerebellum	No: 6.64 (3.93–10.45)	0.300	No: 2041 (1254.75–2629)	0.393
	Yes: 4.6 (1.96–8)	(NS)	Yes: 1347.13 (631.03–2948.5)	(NS)
Pons	No: 6.5 (3.97–9.78)	0.876	No:1981.5(1378.63–2571.75)	0.836
	Yes: 5.23 (1.93–11.03)	(NS)	Yes:1517.23(454.5–4356.5)	(NS)
Thalamus	No: 6.5 (3.97–9.51)	0.959	No:1938(1378.63–2491.5)	0.717
	Yes: 6.53 (1.93–11.03)	(NS)	Yes:2597.63(454.5–4356.5)	(NS)
Medulla	No: 6.3 (3.08–9.59)	0.049	No:1817.5(996.25–2514.5)	0.049
	Yes: 11.03 (7.25–12.8)	(S)	Yes:4356.5(1997.5–4522)	(S)

BDNF: Brain-derived neurotrophic factor; ICAM-1: Intercellular adhesion molecule-1; IQR: Interquartile range; MRI: Magnetic resonance imaging. The brain regions involved show intramyelinic or cytotoxic edema with increased T2-FLAIR signal. *Supratentorial regions include frontal, temporal, parietal, occipital, peri-trigonal, semiovale centrum, and corona radiata. +Basal ganglia comprise the internal capsule, corpus callosum, and other basal ganglia. P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S). • Mann-Whitney test.

Regarding the relationship between BDNF and adaptive behavior/intellectual functioning in the studied patients, no significant differences were detected across IQ classifications (Vineland, verbal, nonverbal, and total IQ) or across CBCL externalizing and total score groups ($p > 0.05$). When Vineland scores were analyzed in four categories, the results were non-significant ($\chi^2 = 6.194$, $p = 0.103$). However, when reclassified into two categories ("below average" vs. "mild–severe ID"), a significant difference emerged ($\chi^2 = 6.020$, $p = 0.049$). Additionally, CBCL internalizing groups showed a significant difference ($\chi^2 = 8.753$, $p = 0.013$), with patients in the clinical range demonstrating higher BDNF levels (median: 11.03) compared to those in the borderline range (median: 2.57) and the normal range (median: 6.54). It is also noteworthy that the mild ID group consistently exhibited lower BDNF values relative to other groups **(Table 7)**. Secondary regrouping of adaptive categories was performed for exploratory analysis to enhance clinical interpretability.

With respect to ICAM-1 and adaptive behavior/intellectual functioning, no significant differences were observed across IQ categories (Vineland, verbal, nonverbal, total IQ) or in CBCL externalizing and total score groups ($p > 0.05$). The only significant finding was within CBCL internalizing groups ($\chi^2 = 8.084$, $p = 0.018$), where patients in the clinical range had markedly higher ICAM-1 levels (median: 2822.5) compared to the borderline group (median: 745.73) and the normal group (median: 2084.5) **(Table 7).**

Table (7): Relation between BDNF, ICAM-1 levels and Adaptive behavior & intellectual functioning among the studied patients.

Outcome Groups	BDNF Median (IQR)	Test value	P-value	Sig.	ICAM-1 Median (IQR)	Test value	P-value	Sig.
Vineland								
Below average	9.93(8.98–10.88)				2509.75(2288.5–2731)			
Mild ID	2.44 (0.91–5.65)	6.194	0.103	NS	1001 (317.81–1800)	5.818	0.121	NS
Moderate ID	6.75 (6.12–7.25)				1780.5 (1698–1997.5)			
Severe ID	8.03 (4–10.63)				2514.5(1502.5–2992.5)			
Below avg vs. Mild–Severe	9.93(8.98–10.88) vs.7(4–9.59)	6.020≠	0.049	S	2509.75 (2288.5–2731) vs. 2041 (1502.5–2584.5)	4.655≠	0.098	NS
Total IQ								
Average	4.2 (1.93–6.47)				1387.25 (454.5–2320)			
Below average	7.56 (1.25–10.45)	0.313≠	0.958	NS	2119.25 (340.33–2822.5)	1.082≠	0.781	NS
Mild ID	3.03 (0.95–11.94)				985.3 (368.42–3881.5)			
Moderate ID	7.12 (2.25–11.44)				2607.73 (746.37–4267.5)			
CBCL Internal								

Normal	6.54 (2.44 – 10.63)				2084.5 (996.25 – 2731)			
Borderline	2.57 (0.91 – 6.12)	8.753≠	0.013	S	745.73 (317.81 – 1698)	8.084≠	0.018	S
Clinical	11.03 (8.76 – 11.08)				2822.5 (2584.5 – 3427.5)			
CBCL External								
Normal	5.06 (1.3 – 10.45)				1600.25 (455.78 – 2514.5)			
Borderline	8.03 (2.44 – 12.8)	1.663≠	0.435	NS	2992.5 (1001 – 4522)	2.758≠	0.252	NS
Clinical	8.76 (5.67 – 9.98)				2360 (1780.5 – 2822.5)			
CBCL Total								
Normal	6.39 (1.3 – 10.63)				1942.25 (455.78 – 2629)			
Borderline	3.21 (0.95 – 4)	1.390≠	0.449	NS	1036.95 (368.42 – 1502.5)	1.922≠	0.383	NS
Clinical	8.03 (3.93 – 9.98)				2360 (1254.75 – 2992.5)			

Regarding the correlation between biomarkers and decompensation frequency, neither BDNF nor ICAM-1 exhibited statistically significant correlations with decompensation episodes ($p > 0.05$ for all) **(Table 8)**.

Table (8): Correlation of BDNF and ICAM-1 levels with decompensation frequency among the studied patients.

Variables	BDNF		ICAM-1	
	r	P-value	r	P-value
Metabolic Decompensation^{+} (n=42)	0.094	0.555	0.149	0.347

BDNF: brain-derived neurotrophic factor; ICAM-1: intracellular adhesion molecule 1; +necessitates NICU or PICU admission*: Significant; **: Highly significant Spearman correlation coefficient.

4. Discussion

Maple Syrup Urine Disease belongs to the group of intoxication-type inborn errors of metabolism, and even under strict dietary management and regular medical supervision, many affected children continue to experience psychomotor delay as well as cognitive, behavioral, and psychiatric difficulties. Early diagnosis through newborn screening and careful long-term monitoring remain essential to reduce these complications **(Castells et al., 2019).**

The present study demonstrated markedly elevated serum Brain-Derived Neurotrophic Factor (BDNF) and Intercellular Adhesion Molecule-1 (ICAM-1) levels in MSUD patients compared to healthy controls, supporting their potential role as biomarkers of MSUD pathophysiology.

Our observation of markedly elevated BDNF in MSUD patients contrasts with earlier reports. **Scaini et al. (2018)** reported reduced plasma BDNF in MSUD compared with controls, while **Castells et al. (2019),** in a cohort of mixed aminoacidopathies including MSUD, found no significant difference. The nearly 14-fold increase observed in our study suggests that BDNF upregulation may represent an active compensatory response to persistent metabolic and neuroinflammatory stress. Similar stage-dependent patterns have been described in other neurological disorders, including increased BDNF in treated phenylketonuria patients reported by **Faverzani et al. (2023)** and transient BDNF elevation during the biologically active

phase of early Alzheimer's disease prior to subsequent decline, as observed by **Gao et al. (2022).**

In contrast, our findings for Intercellular Adhesion Molecule-1 (ICAM-1) are consistent with previous literature. **Scaini et al. (2018)** similarly documented significantly elevated soluble ICAM-1 levels in Maple Syrup Urine Disease patients, linking these elevations to recurrent metabolic crises and ongoing inflammatory activity. Comparable increases in ICAM-1 have also been reported in other central nervous system disorders, including dementia **(Müller, 2019),** as well as in both unipolar and bipolar depression **(Müller, 2019; Pantovic-Stefanovic et al., 2024).**

In the present cohort, abnormal Brain Magnetic Resonance Imaging (MRI) findings were documented in 66.7% of the imaged patients (20/30), consistent with previous reports demonstrating frequent brain neuroimaging abnormalities in MSUD **(Cheng et al., 2017; Ali et al., 2022)**. Supratentorial white-matter involvement was the most common pattern, aligning with the diffuse white-matter abnormalities described in classic and variant MSUD phenotypes **(Cheng et al., 2017).** Brainstem involvement was additionally identified in a subset of patients. Although many imaging studies emphasize midbrain and pontine abnormalities, brainstem structures as a whole are recognized as metabolically vulnerable regions in MSUD, likely due to early myelination and high metabolic demand **(Li et al., 2021; Ibrahim et al., 2014).**

Patients with medullary involvement demonstrated higher serum BDNF and ICAM-1 levels, indicating a possible association between brainstem structural changes and neuroinflammatory and neurotrophic activity. However, this relationship reached only borderline statistical significance ($p = 0.049$) and involved a very small subgroup. The limited number of affected cases reduces the robustness of this finding. Accordingly, the observed association should be considered preliminary and requires confirmation in larger cohorts before inferring region-specific biomarker elevation.

Moreover, patients exhibiting internalizing psychiatric symptoms demonstrated higher BDNF and ICAM-1 concentrations, suggesting that neuroinflammatory mechanisms may contribute not only to structural injury but also to emotional and behavioral dysregulation.

On the other hand, neither BDNF nor ICAM-1 levels correlated significantly with the frequency of metabolic decompensation episodes. This suggests that biomarker elevation reflects a persistent neurobiological stress state rather than acute episodic crises, with BDNF representing a compensatory neuroprotective response to ongoing metabolic injury and ICAM-1 reflecting sustained endothelial activation and low-grade neuroinflammation, both more closely tied to chronic brain adaptation than to the cumulative burden of decompensation events.

This study has several notable strengths. It represents the first Egyptian cohort to investigate BDNF and ICAM-1 in MSUD, offering valuable insights from a population with high consanguinity. Importantly, it combined biochemical,

neurodevelopmental, and behavioral assessments within the same group, allowing exploration of how these biomarkers relate not only to metabolic control but also to adaptive functioning, intellectual outcomes, and psychiatric symptoms. This integrated approach goes beyond descriptive biomarker profiling by uncovering selective associations that may inform long-term neurological risk stratification and guide translational applications in MSUD care.

This study also carries several limitations. The sample size was small. Biomarker measurements were performed at single time points. Finally, the absence of longitudinal follow-up restricts interpretation of causality between biomarker elevations and neurodevelopmental or psychiatric outcomes.

The elevated levels of BDNF and ICAM-1, particularly in association with brainstem abnormalities and internalising behaviours, hold promise as tools for monitoring neurological injury in MSUD. Future longitudinal studies are warranted to validate their clinical utility and explore their potential in guiding therapeutic strategies.

5. Conclusion

BDNF and ICAM-1 levels may provide insight into neuroinflammatory processes in MSUD and could be integrated into comprehensive patient monitoring strategies.

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Figure 1: Clinical phenotype distribution of the study cohort. Pie chart illustrating the distribution of clinical phenotypes among patients with maple syrup urine disease (MSUD). Classic MSUD was the predominant phenotype, accounting for 88.0% of cases, whereas intermediate and intermittent MSUD represented 7.1% and 4.8% of cases, respectively.

Figure (2): Distribution of brain magnetic resonance imaging (MRI) findings among patients with maple syrup urine disease (MSUD). Brain MRI was normal in 33.3% of patients. Among those with abnormal MRI findings, supratentorial white matter abnormalities were the most common (56.7%), followed by basal ganglia involvement (33.3%), midbrain abnormalities (30.0%), pontine and thalamic involvement (20.0% each), cerebellar abnormalities (13.3%), medullary involvement (10.0%), and partial empty sella with optic nerve sheath ectasia and retrocerebellar cystic lesion (likely arachnoid cyst) (3.3% each). Percentages represent the proportion of the study cohort; patients may have had abnormalities involving more than one brain region.