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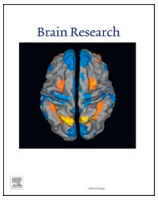

Research report

Serum tyrosine is associated with better cognition in Lewy body dementia

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ABSTRACT

Amino acids' neuroactivity, and roles in excitotoxicity and oxidative stress are linked to dementia. We aimed to investigate whether circulating amino acid concentrations were associated with cognitive decline in patients with mild Alzheimer's disease (AD) and Lewy body dementia (LBD). Baseline serum amino acid concentrations were measured in 89 patients with AD and 65 with LBD (13 with Parkinson's disease dementia and 52 with dementia with Lewy bodies). The Mini-Mental State Examination (MMSE) was administered at baseline and annually for five years. Associations between baseline amino acid concentrations and longitudinal MMSE score were assessed using a linear-mixed effects model stratified by diagnosis with adjustment for multiple comparisons. The results of the study indicated that serum tyrosine was positively associated with MMSE performance during the five-year follow-up period in patients with LBD (q-value = 0.012), but not AD. In conclusion, higher baseline serum concentrations of tyrosine, the precursor amino acid in dopamine and norepinephrine synthesis, was associated with better cognitive performance in patients with LBD, but not AD, throughout the 5-year follow-up period.

1. Introduction

Predicting the rate of cognitive deterioration represents a major challenge in neurodegenerative disorders (Holtzer, 2008; Bennett, 2005; Schneider, 2012). This has driven a search for biomarkers and underlying mechanisms that can determine prognosis and help select patients for targeted treatment approaches (Mayeux, 2004).

Metabolomic studies have demonstrated perturbations in neurotransmitter and amino acid metabolism in neurodegeneration (Gonzalez-Dominguez, 2015). Significantly, both the brain and peripheral organs show altered amino acid homeostasis in mouse models of Alzheimer's disease (AD) (Lin, 2014; Gonzalez-Dominguez, 2015), highlighting the potential importance of changes in amino acid metabolism outside the brain. Importantly, amino acids are transported over the semipermeable blood–brain barrier (BBB) and brain serotonin synthesis for example is dependent on tryptophan availability (Fernstrom, 1988).

Studies have linked glutamate, aspartate, the branched-chain (valine, leucine, isoleucine) and aromatic amino acids (tyrosine, tryptophan, phenylalanine) to AD (Gonzalez-Dominguez et al., 2015; Hudd, 2019; Tynkkynen, 2018) and neurotransmitter synthesis and function (Fernstrom, 2013), excitotoxicity, neural oxidative stress, and apoptosis (Jouvet, 2000; Wang and Reddy, 2017). Amino acid precursors of neurotransmitters may differentially affect neurodegenerative diseases with distinct etiologies according to the neurotransmitter systems mostly involved, for example dopamine and Parkinson's disease (PD). Thus, a key question is whether amino acids are differentially associated with cognitive prognosis in dementia according to the underlying disease.

We recently demonstrated that catabolites of the tryptophan degradation pathway, the kynurenines, were associated with cognitive function and neuropsychiatric symptoms in patients with dementia (Hafstad Solvang, 2019). In the present study, we sought to further investigate the circulating amino acid profile of patients with AD and Lewy body dementia (LBD) in relation to their cognitive prognosis over five years of follow-up.

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2. Results

2.1. Cohort characteristics

The patients were on average 75 years old at study baseline. The AD and LBD groups were comparable concerning age, MMSE and GFR at baseline, although more female patients had AD (67%) compared to LBD (42%) (Table 1).

2.2. Serum amino acids and dementia diagnosis

Circulating concentrations of glutamate and aspartate were higher in patients with AD, while serum ornithine was higher in LBD (Table 2). However, these differences were not significant following adjustment for multiple comparisons.

2.3. Serum tyrosine is associated with improved MMSE performance in Lewy body dementia

The association between MMSE performance and tyrosine in patients with LBD was significant after adjustment for multiple comparisons (Est. [95% CI]: 1.37 [0.65, 2.08], unadjusted p-value = 0.00019, adjusted q-value = 0.012), with higher tyrosine levels at baseline being associated with higher MMSE score during the five-year study period, see Table 3 and Fig. 1. Further, the interaction between diagnosis and tyrosine was also significant (p = 0.007), showing a significantly different association in LBD compared to AD. Serum tyrosine did not affect the rate of MMSE decline in either subgroup, and no other significant associations between amino acids and cognition were found.

2.4. Post-hoc analyses

We studied the association between tyrosine and MMSE decline in patients with and without dopaminergic anti-Parkinson medication at baseline. Tyrosine was associated with the MMSE intercept both in the 18 patients using anti-Parkinson medications (12 with Parkinson's disease dementia and 6 with dementia with Lewy bodies) at baseline (Est. 1.21, 95% CI [0.25–2.06], p = 0.006) and in those not using such medications (Est. 1.42, 95% CI [0.64–2.19], p < 0.001). In addition, we included adjusted analyses to evaluate potential tyrosine-psychotropic drug use confounding if the drug was used at the time of baseline blood sampling (Table 4). No confounding was observed.

3. Discussion

In the present study, higher serum concentrations of tyrosine at baseline, the precursor amino acid in dopamine synthesis (Molinoff and Axelrod, 1971), was associated with better performance on the MMSE in patients with LBD, but not AD, throughout the 5-year follow-up period.

Higher concentrations of serum tyrosine were only significantly associated with better cognitive performance in LBD, despite similar tyrosine levels in AD (66 μmol/L) and LBD (71 μmol/L). Our LBD observation is in line with dietary studies in healthy persons where higher habitual tyrosine intake has been linked to improved cognitive performance in both younger and older adults (Kuhn, 2019). Oral supplementation of tyrosine has also been found to nullify the negative effects of stress, induced by conditions such as extreme weather or increasing cognitive workload, on working memory and information processing. These acute buffering effects may be related to tyrosine's ability to neutralize/replenish the brains depleted catecholamine levels (Hase et al., 2015).

The defining feature of LBD is α-synuclein pathology, which is particularly toxic to dopaminergic neurons, (Spillantini, 1997; Yu et al., 2005). Furthermore, α-synuclein pathologies lead to severe deficits in norepinephrine, a neurotransmitter increasingly linked to cognitive function, due to early damage to the locus coeruleus (Del Tredici and Braak, 2013; Cools and D'Esposito, 2011). Evidence suggests α-synuclein inhibits the activities of both tyrosine hydroxylase (TH), which hydroxylates tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), and aromatic amino acid decarboxylase (AAAD), which catalyzes the conversion of L-DOPA to dopamine (Gao, 2007; Tehranian, 2006). The synthesis of catecholamine neurotransmitters in the brain depends on circulating tyrosine, which is transported from peripheral blood to the brain. However, it is assumed that TH, the rate-limiting enzyme in dopamine synthesis, operates close to full saturation from tyrosine under normal conditions suggesting, increased tyrosine availability would not substantially impact dopamine synthesis (Brady, 2011). This view has however been challenged by human studies suggesting an effect in neurotransmitter depleted states (Hase et al., 2015), with one study finding evidence of increased dopamine synthesis in patients with PD following tyrosine supplementation (Growdon, 1982).

There is some evidence supporting the benefit of levodopa treatment in LBD (Stinton, 2015) but there are concerns about negative effects on cognition and neuropsychiatric symptoms. Our observational study cannot discern the reason for the association between higher serum tyrosine and improved cognitive outcomes in LBD. Several studies do point to a potential lack of efficacy for tyrosine in replenishing catecholamines (Brady, 2011). A hypothesis postulating that increased tyrosine availability could increase the activity of TH in LBD patients

Table 1
Cohort characteristics.

	All	AD	LBD	p-value
Age, m (SD)	74.9 (7.4)	75.0 (7.8)	74.6 (6.8)	0.701[a]
Female, n [%]	87 (56.5)	60 (67.4)	27 (41.5)	0.001*[b]
MMSE, m (SD)	23.7 (2.8)	23.5 (2.5)	23.9 (3.1)	0.314[a]
GFR[c], m (SD)	79.1 (20.3)	78.0 (20.3)	80.6 (20.3)	0.448[b]

All participants, *n* 154. Abbreviations: AD, Alzheimer's disease (*n*, 89); GFR, glomerular filtration rate; LBD, Lewy body dementia (*n*, 65); m, mean; MMSE, Mini-Mental State Examination; SD, standard deviation.
*p < 0.05.
[a] Pearson's Chi Square test.
[b] Student's T-test.
[c] In milliliters per minute per 1.73 square meters of body surface area.

Table 2
Serum amino acid concentrations[a] by diagnosis.

		All	AD	LBD	p-value[b]
Glycine	Gly	345 [132]	354 [126]	335 [145]	0.099
Serine	Ser	148 [41]	152 [37]	146 [41]	0.196
Glutamine	Gln	626 [103]	620 [73]	630 [136]	0.360
Aspargine	Asn	57 [12]	57 [12]	57 [11]	0.516
Threonine	Thr	133 [41]	126 [35]	141 [49]	0.110
Cysteine	tCys	337 [55]	339 [54]	337 [55]	0.822
Methionine	Met	27 [7.9]	27 [7.4]	28 [8.6]	0.375
Proline	Pro	204 [92]	200 [88]	210 [85]	0.360
Histidine	His	78 [14]	78 [13]	79 [13]	0.964
Ornithine	Orn	90 [31]	86 [26]	95 [34]	0.027*
Lysine	Lys	186 [44]	185 [37]	188 [53]	0.371
Arginine	Arg	123 [31]	124 [28]	122 [31]	0.404
Tryptophan	Trp	66 [22]	66 [22]	67 [16]	0.871
Glutamate	Glu	77 [39]	80 [37]	68 [41]	0.020*
Aspartate	Asp	39 [19]	44 [18]	35 [14]	0.003*
Tyrosine	Tyr	67 [25]	66 [21]	71 [32]	0.258
Alanine	Ala	410 [124]	417 [111]	407 [138]	0.828
Phenylalanine	Phe	87 [27]	88 [28]	86 [22]	0.526
Leucine	Leu	128 [38]	127 [29]	130 [36]	0.379
Valine	Val	239 [60]	231 [57]	249 [60]	0.259
Isoleucine	Ile	63 [24]	58 [20]	67 [23]	0.136

All participants, *n* 154. Abbreviations: AD, Alzheimer's disease (*n*, 89); LBD, Lewy Body Dementia (*n*, 65).
*p < 0.05.
[a] Amino acid concentrations in μmol/L reported as medians and interquartile range.
[b] Mann-Whitney U Test.

Table 3
Amino acids and MMSE test performance over 5 years for all patients and by diagnosis.

	All[a]		AD[b]		LBD[b]	
	Est [95% CI]	p	Est. [95% CI]	p	Est. [95% CI]	p
Gly	−0.02 [−0.55, 0.52]	0.955	−0.04 [−0.74, 0.66]	0.915	−0.17 [−0.97, 0.63]	0.675
Ser	0.22 [−0.29, 0.73]	0.399	0.32 [−0.22, 0.86]	0.244	−0.10 [−1.14, 0.95]	0.855
Gln	0.07 [−0.46, 0.59]	0.807	0.08 [−0.55, 0.70]	0.811	0.22 [−0.66, 1.09]	0.627
Asn	0.31 [−0.21, 0.83]	0.241	0.08 [−0.56, 0.72]	0.803	0.62 [−0.20, 1.44]	0.136
Thr	0.15 [−0.37, 0.67]	0.576	−0.06 [−0.69, 0.57]	0.843	0.48 [−0.34, 1.30]	0.251
tCys	−0.57 [−1.19, 0.05]	0.071	0.04 [−0.68, 0.76]	0.913	−1.34 [−2.50, −0.19]	0.023*
Met	0.39 [−0.13, 0.90]	0.143	0.21 [−0.43, 0.85]	0.524	0.74 [−0.06, 1.54]	0.071
Pro	0.12 [−0.43, 0.67]	0.666	−0.23 [−0.87, 0.40]	0.471	0.69 [−0.21, 1.59]	0.136
His	0.31 [−0.20, 0.83]	0.234	0.30 [−0.29, 0.89]	0.318	0.54 [−0.40, 1.47]	0.262
Orn	0.18 [−0.34, 0.71]	0.498	0.12 [−0.47, 0.72]	0.682	0.49 [−0.43, 1.41]	0.295
Lys	−0.16 [−0.68, 0.36]	0.546	−0.14 [−0.78, 0.51]	0.681	0.14 [−0.71, 0.99]	0.752
Arg	−0.09 [−0.63, 0.45]	0.755	−0.21 [−0.85, 0.42]	0.509	0.27 [−0.66, 1.21]	0.564
Trp	0.20 [−0.31, 0.72]	0.439	0.13 [−0.45, 0.71]	0.659	0.58 [−0.33, 1.48]	0.210
Glu	0.09 [−0.44, −0.63]	0.732	0.10 [−0.56, 0.75]	0.773	0.09 [−0.78, 0.95]	0.847
Asp	0.21 [−0.33, 0.76]	0.443	0.26 [−0.41, 0.93]	0.447	0.12 [−0.75, 0.99]	0.786
Tyr	0.70 [0.19, 1.21]	0.008*	0.06 [−0.61, 0.74]	0.855	1.37 [0.65, 2.08]	<0.001[+]
Ala	0.41 [−0.13, 0.95]	0.133	−0.01 [−0.68, 0.65]	0.970	0.86 [0.14, 1.77]	0.022*
Phe	0.58 [0.04, 1.12]	0.037*	0.63 [0.03, 1.23]	0.040*	0.68 [−0.32, 1.38]	0.182
Leu	0.25 [−0.28, 0.79]	0.353	0.01 [−0.63, 0.65]	0.983	0.78 [−0.07, 1.63]	0.073
Val	0.12 [−0.42, 0.66]	0.655	−0.03 [−0.64, 0.57]	0.911	0.71 [−0.23, 1.65]	0.139
Ile	0.34 [−0.19, 0.88]	0.211	0.03 [−0.64, 0.70]	0.929	0.87 [0.05, 1.69]	0.039*

Abbreviations: AD, Alzheimer's disease; LBD, Lewy Body Dementia, see Table 2 for amino acid abbreviations.
*$p < 0.05$.
[a] Linear mixed-effects model with age, gender, time, diagnosis, GFR, age*time and diagnosis*time.
[b] Linear mixed-effects model stratified by diagnosis with age, gender, time, GFR and age*time.
[+] FDR: significant after adjustment for multiple comparisons using a false discovery rate based method.

should be tested by measuring biomarkers of dopamine and norepinephrine synthesis before and after supplemental tyrosine compared to placebo. If there were such an effect, a clinical trial investigating tyrosine supplementation would be warranted to explore if this milder approach to increasing neurotransmitter levels improves cognition with less risk for neuropsychiatric and other dopaminergic side-effects compared to levodopa treatment.

The present study has a number of strengths including its longitudinal design with annual follow-up examinations until death, a low dropout rate among the participants, and centralized laboratory analyses of all metabolites. The main limitations are a relatively small sample size, absence of an age-matched longitudinal control group, and a lack of ability to identify causal relationships, common to all observational studies. The serum amino acid profile was measured at baseline only, nonetheless, a single measurement of tyrosine in fasting serum samples has previously been shown to have good reliability over time, reflected by an intraclass correlation coefficient of $\geq$ 0.5 (Carayol, 2015). As tyrosine is an essential amino acid, the study would have also benefited from collection of dietary intake data at baseline and annually. However, it should be noted that serum tyrosine levels did not differ between groups at baseline. Diagnosis was clinical, but post-mortem pathological diagnosis has been found to be consistent with the clinical diagnosis in more than 80% of cases (Skogseth, 2017). In addition, the study would be greatly strengthened by assessment of amino acids in CSF and/or brain samples.

4. Conclusion

To conclude, higher serum concentrations of tyrosine, the precursor amino acid in dopamine and norepinephrine synthesis, was associated with better cognitive performance in patients with LBD, but not AD, throughout the 5-year follow-up period. Serum tyrosine did not affect the rate of MMSE decline in either subgroup, and no other significant associations between amino acids and cognition were found. Our observational study suggests tyrosine supplementation could potentially benefit those with mild LBD; however, this must first be further investigated in clinical intervention studies aimed at improving cognition in dementia.

5. Materials and methods

5.1. Study participants

One hundred and fifty-four patients with AD (*n* 89) and LBD (*n* 65; 13 with Parkinson's disease dementia and 52 with dementia with Lewy bodies) from the Dementia Study of Western Norway (DemVest), a multicenter longitudinal cohort study with annual follow-up for five years or until death, were sampled. Details of the study procedures are described elsewhere (Aarsland, 2008). Briefly, diagnosis followed structured interviews, and clinical examination, including a standardized neuropsychological test battery and a neuropsychiatric assessment. Thyroid disorders and vitamin B_{12} deficiency were ruled out by routine blood tests, and disorders such as brain tumors and hydrocephalus were ruled out using structural neuroimaging. Only patients with mild dementia at the study baseline were included, which was defined as a Mini-Mental State Examination (MMSE) score $\geq$20 or a Clinical Dementia Rating Scale (CDR) $\geq$1. The study recruited patients from 2005 to 2012, with selective recruitment of LBD from 2007 onwards.

As dementia with Lewy bodies (DLB) and Parkinson's Disease Dementia (PDD) are neuropathologically highly similar, they are considered as one disorder in the present study (i.e. LBD) (McKeith, 2017). AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann, 1984). LBD was diagnosed according to the 2005 revised criteria for DLB (McKeith, 2005) and the Movement Disorders Society criteria for PDD (Duyckaerts and Hauw, 1997). Exclusion criteria were acute delirium at the time of inclusion, previous bipolar or psychotic disorders, terminal illness or major somatic illness such as active cancer, end-stage heart and renal failure. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) study equation (Levey, 2002). This research was performed in accordance with the declaration

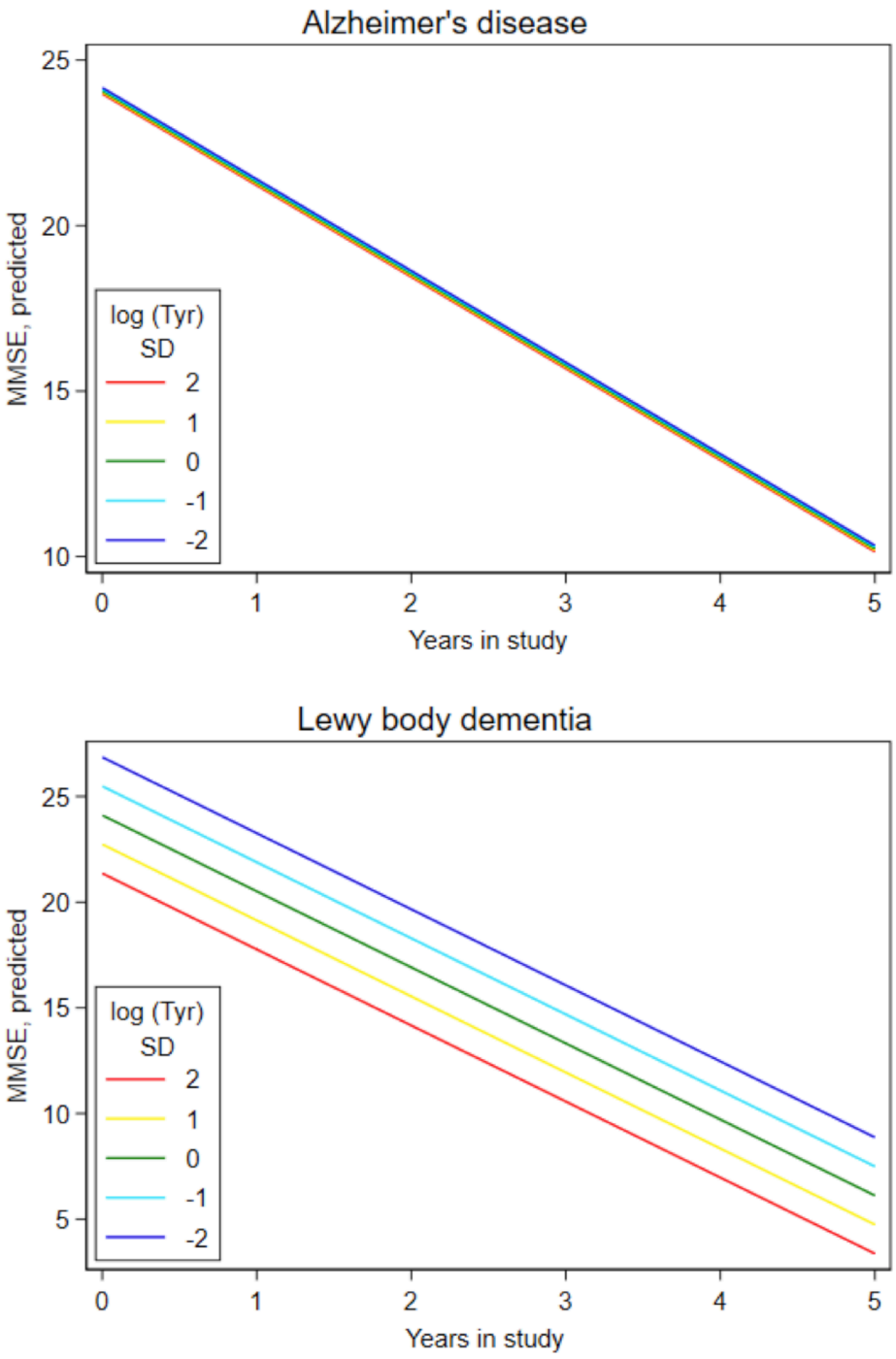

Fig. 1. Tyrosine and MMSE performance in Alzheimer's disease and Lewy body dementia. The MMSE trajectories per 1 standard deviation (SD) from the mean of log-transformed tyrosine levels are displayed according to diagnosis (marginal predictions from the linear mixed-effects model adjusted for age, gender, time, GFR and age*time interaction). As can be readily seen, there was close to no effect in Alzheimer's disease, which stands in stark contrast to the dose–response effect in Lewy body dementia. There was no impact on the rate of decline and the association between 5-year cognitive prognosis and baseline tyrosine levels is thus similar throughout the study. Abbreviation: MMSE, Mini-Mental State Examination.

of Helsinki and the Regional Committee for Medical and Health Research Ethics approved the study (REC number: 2010/663). All patients provided written consent after being explained the details of the study in the presence of a caregiver.

5.2. Analysis of serum amino acids

Fasting serum samples were collected at baseline according to standardized procedures as previously described (Aarsland, 2008) and stored at −80 °C until analyses. The concentrations of amino acids in serum were measured by gas chromatography-tandem mass spectrometry (GC–MS/MS) based on methylchloroformate derivatization (Midttun, 2016). The within-day coefficient of variation ranged from 1 to 3% and the between-day coefficient of variation ranged from 2 to 4%.

5.3. Cognitive assessment

The MMSE has been evaluated to have adequate construct and criterion validity in detecting cognitive impairment, and correlates with measures of neuropathological severity postmortem, most so with cortical neurofibrillary tangle pathology (Nelson et al., 2009). The mean annual decline has been estimated at 3.3 points per year (Han, 2000), with a change of 2–4 points representing a reliable change (Hensel et al., 2007), and the scale has also been shown to be a good measure of cognitive decline in LBD (Biundo, 2016). We used five-year MMSE data in this study to avoid major issues associated with floor effects among

Table 4
Tyrosine according to psychotropic medications and adjusted analyses.

							Model[c]	FE	95% CI	p
All (n = 152)							0	0.71	0.20, 1.21	.006*
AD (n = 89)							0	0.06	-0.60, 0.72	.857
LBD (n = 63)							0	1.39	0.68, 2.10	<.001**
		Not using medication		**Using medication**						
		n	**Tyrosine[a]**	**N**	**Tyrosine[a]**	**p[b]**				
Anti-dementia										
All		82	68.9 ±26	70	66.4 ±25	.935	1	0.71	0.21, 1.22	.006
AD		46	67.4 ±34	43	64.7 ±19	.522	1	0.07	-0.59, 0.73	.842
LBD		36	71.1 ±34	27	73.0 ±31	.514	1	1.48	0.77, 2.18	<.001**
	AChEI									
	All	84	67.8 ±26	68	67.1 ±26	.840	1	0.71	0.21, 1.22	.006*
	AD	47	67.3 ±23	42	64.5 ±19	.522	1	0.06	-0.60, 0.72	.850
	LBD	37	70.6 ±34	26	73.9 ±30	.295	1	1.48	0.77, 2.19	<.001**
	NMDAR-AA									
	All	149	67.4 ±26	3	65.6 ±9.3	.942	2	0.71	0.21, 1.21	.005*
	AD	88	65.9 ±33	1	65.6 ±NA	NA	2	0.06	-0.60, 0.72	.860
	LBD	61	71.5 ±32	2	68.3 ±9.3	.742	2	1.37	0.67, 2.08	<.001**
Anti-depressants										
All		99	66.8 ±21	53	73.0 ±30	.103	1	0.74	0.22, 1.25	.005*
AD		56	64.5 ±13	33	69.7 ±28	.149	1	0.09	-0.58, 0.76	.796
LBD		43	67.9 ±34	20	76.4 ±28	.425	1	1.38	0.67, 2.10	<.001**
	SSRI									
	All	112	66.9 ±22	40	73.2 ±28	.132	1	0.74	0.24, 1.25	.004*
	AD	65	64.3 ±14	24	72.6 ±28	.112	1	0.11	-0.55, 0.78	.736
	LBD	47	70.1 ±33	16	74.6 ±27	.705	1	1.39	0.68, 2.10	<.001**
	SNRI									
	All	148	67.5 ±25	4	60.5 ±32	.573	2	0.70	0.18, 1.21	.008*
	AD	87	65.6 ±24	2	58.6 ±17	.347	2	0.07	-0.60, 0.73	.848
	LBD	61	71.5 ±29	2	77.5 ±47	.814	2	1.37	0.64, 2.09	<.001**
	Tetracyclic									
	All	135	67.4 ±24	17	63.3 ±35	.799	2	0.69	0.16, 1.21	.011*
	AD	78	66.3 ±19	11	63.3 ±38	.425	2	0.04	-0.67, 0.75	.910
	LBD	57	71.5 ±27	6	66.9 ±35	.623	2	1.30	0.55, 2.06	<.001**
Anti-psychotics										
All		139	67.4 ±26	13	66.4 ±13	.867	2	0.69	0.18, 1.21	.008*
AD		84	65.9 ±22	5	65.6 ±30	.336	2	0.14	-0.53, 0.82	.678
LBD		55	73.0 ±32	8	67.0 ±14	.397	2	1.30	0.59, 2.01	<.001*
Anti-Parkinson										
All		134	67.2 ±25	18	73.0 ±35	.964	2	0.59	0.05, 1.13	.031*
AD		89	65.6 ±22	0	NA	NA	2	NA	NA	NA
LBD		45	70.1 ±27	18	73.0 ±34.5	.553	2	1.37	0.54, 2.19	.001*
Benzodiazepines										
All		135	67.5 ±26	17	66.4 ±27	.845	2	0.57	0.05, 1.09	.030*
AD		80	66.3 ±22	9	63.6 ±23	.765	2	0.01	-0.69, 0.72	.974
LBD		55	72.3 ±32	8	69.0 ±30	.951	2	1.12	0.43, 1.82	.002*
Hypnotics										
All		136	68.1 ±27	16	63.0 ±12	.162	2	0.71	0.20, 1.21	.006*
AD		79	67.1 ±24	10	61.2 ±15	.264	2	0.23	-0.48, 0.94	.526
LBD		57	73.0 ±32	6	65.0 ±5.5	.337	2	1.12	0.46, 1.79	.001*

Abbreviations: AChEI, acetylcholine esterase inhibitors; AD, Alzheimer's disease; CI, 95% confidence interval; FE, fixed effect; LBD, Lewy body dementia, n = number of participants; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

* $p < 0.05$, ** $p < 0.001$.

[a] Median ± interquartile range of serum tyrosine in μmol/L.

[b] Testing the hypothesis of a significant difference between patients with or without medications using the Mann-Whitney *U* test.

[c] Model: All models are random coefficient models with MMSE as the outcome, adjusted for only age, gender and time-in-study due to sample size and: Model 0: Tyrosine only. Model 1: Tyrosine and medication (adjusted model) and Model 3: Stratified model with tyrosine excluding the patients on medications due to few persons using medication.

patients with severe dementia.

5.4. Statistics

Differences between AD and LBD in serum amino acid concentrations at the study baseline were tested using the non-parametric Mann-Whitney *U* test, reporting medians and interquartile ranges. For multivariate longitudinal analyses, all amino acid concentrations were log-transformed and standardized (i.e. scaled to z-scores) to achieve comparable effect sizes. We applied a linear mixed-effects model with MMSE scores as the outcome, a linear effect of time (years in study) with random intercepts and slopes, and an unstructured variance–covariance matrix as determined by the Bayesian Information Criterion (BIC). Potential confounders included age, gender and GFR, other independent variables such as amino acids, time, and significant interactions with time (age and diagnosis) were also included. The model was evaluated overall, and stratified according to AD and LBD. We measured 21 amino acids, and thus adjusted the nominal α of 0.05 for multiple comparisons using a distribution tail-based false discovery rate approach for non-independent predictors (R-package: FDRtool (Strimmer, 2008). Post-hoc, we performed adjusted analyses to investigate the association between tyrosine and MMSE decline in patients with and without dopaminergic anti-Parkinson medication at baseline, as well as investigate the potential for baseline serum tyrosine -psychotropic medication

confounding. All analyses were conducted using Stata 16. StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

Declaration of Competing Interest

This paper represents independent research and the views expressed are those of the author(s) and not necessarily those of the funders. Dr Aarsland has received research support and/or honoraria from AstraZeneca, H. Lundbeck, Novartis Pharmaceuticals and GE Health, and served as paid consultant for H. Lundbeck, Eisai, Heptares, Mentis Cura, and Biogen. Dr Aarsland is a Royal Society Wolfson Research Merit Award Holder and would like to thank the Wolfson Foundation and the Royal Society for their support. The other authors of this manuscript have no conflicts of interest to declare.

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Authors' role

DA, JEN and LMG conceptualized the study. AMC and PMU performed formal analysis for biomarkers. LMG and SHS performed the data curation, and formal analyis of all study data. DA provided critical feedback for investigation and methodology. AMC and LMG prepared writing of original draft and visualization of figures and tables. LMG, AMC, DA, PMU, SHS and JEN critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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