Neurochemicals pathways are altered in Amyotrophic lateral sclerosis

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BACKGROUND AND AIM

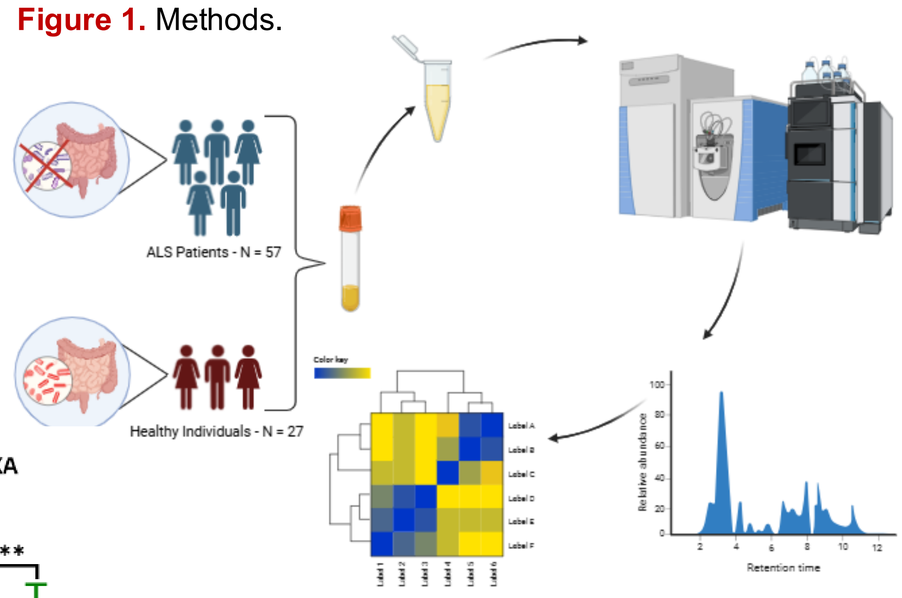
Several studies have confirmed that amyotrophic lateral sclerosis (ALS) patients have a significantly different gut microbiota composition compared to healthy controls (HC). The gut microbiota is responsible for the synthesis of key neurochemicals, such as neurotransmitters, which may potentially serve as biomarkers, prognostic indicators, or treatment targets.

In this research we investigated the levels of circulating neurotransmitters and precursors in ALS patients and matched HC through the targeted quantification of 60 molecules.

METHODS

57 ALS patients and 27 HC were enrolled. Plasma samples were collected and circulating levels of 60 molecules (neurotransmitters and their precursors) were quantified using high-performance liquid chromatography-mass spectrometry.

Figure 1. Methods.



RESULTS

- Plasma levels of **serotonin** were significantly lower in ALS patients. Serotonin plays crucial roles in the body, including sleep, mood, learning, and memory. We found significantly higher TMAO levels in ALS compared to HC: elevated TMAO levels have been associated to cardiovascular risk and inflammation.
- **Xanthurenic acid** levels were lower in ALS: the molecule affects both brain function and neurotransmission through interactions with metabotropic glutamate receptors as lower levels may lead to reduced regulatory effect of on the receptors, of which ALS is characterized by glutamate excitotoxicity. Xanthurenic acid affects both brain function and neurotransmission through interactions with metabotropic glutamate receptors as lower levels may lead to reduced regulatory effect of on the receptors, of which ALS is characterized by glutamate excitotoxicity.
- **Indole-3-propionic acid** were lower in ALS. Indole-3-propionic acid has neuroprotective effects, owing to its anti-inflammatory and antioxidant properties, indicating increased CNS inflammation.
- Higher **AFMK** levels in ALS compared to HC, possibly due to increased ROS and RNS in ALS, which could enhance the conversion of melatonin to AFMK as a protective response

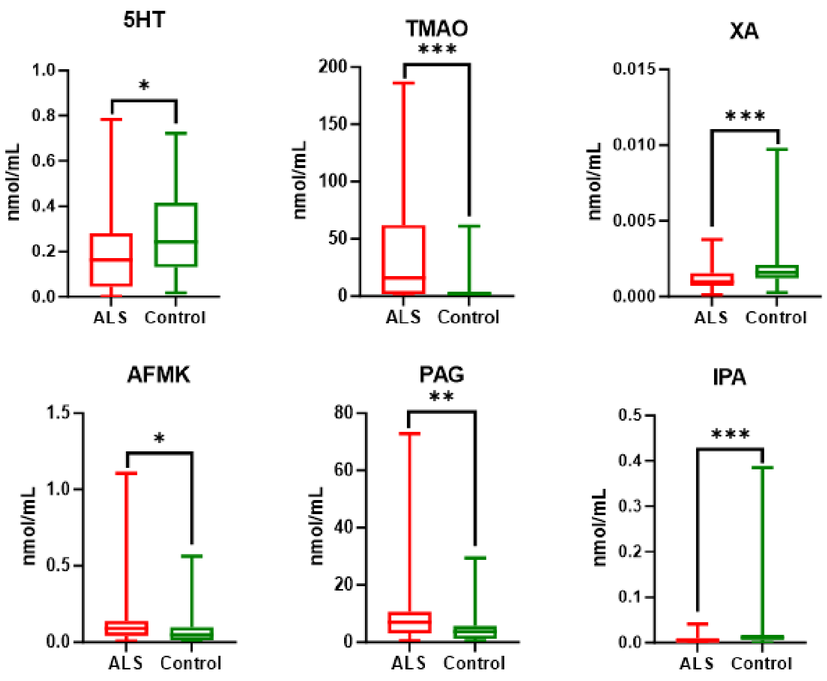


Figure 2. Significant plasma neurochemicals between ALS patients and healthy individuals measured using LC-MS. Comparisons performed using the unpaired non-parametric Mann-Whitney test.

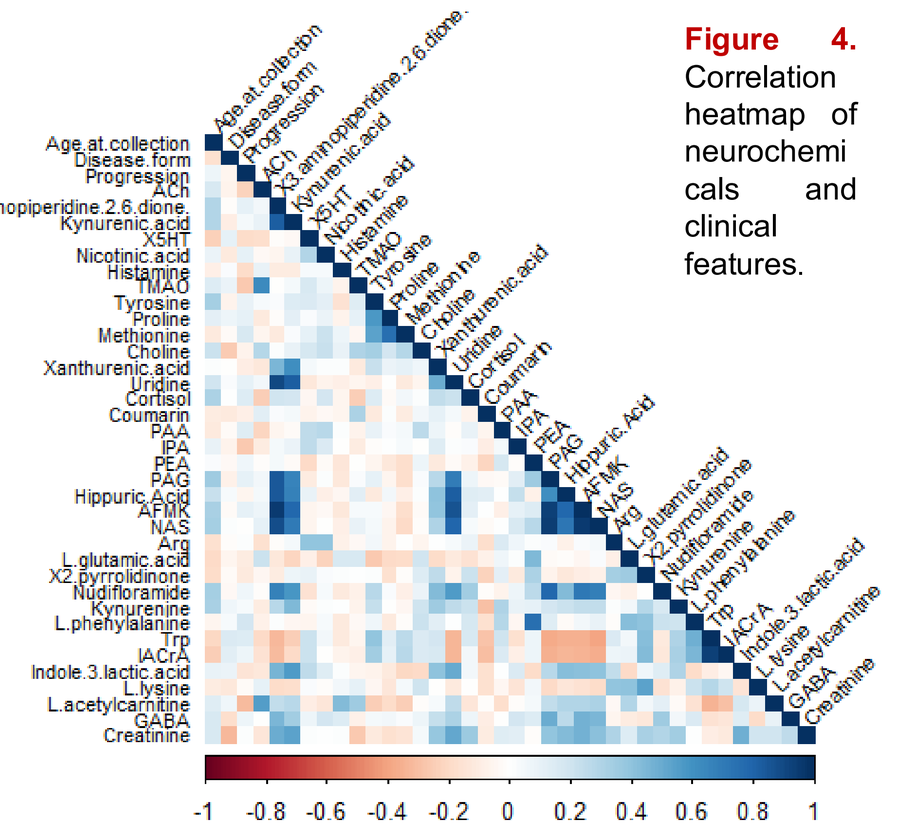


Figure 4. Correlation heatmap of neurochemicals and clinical features.

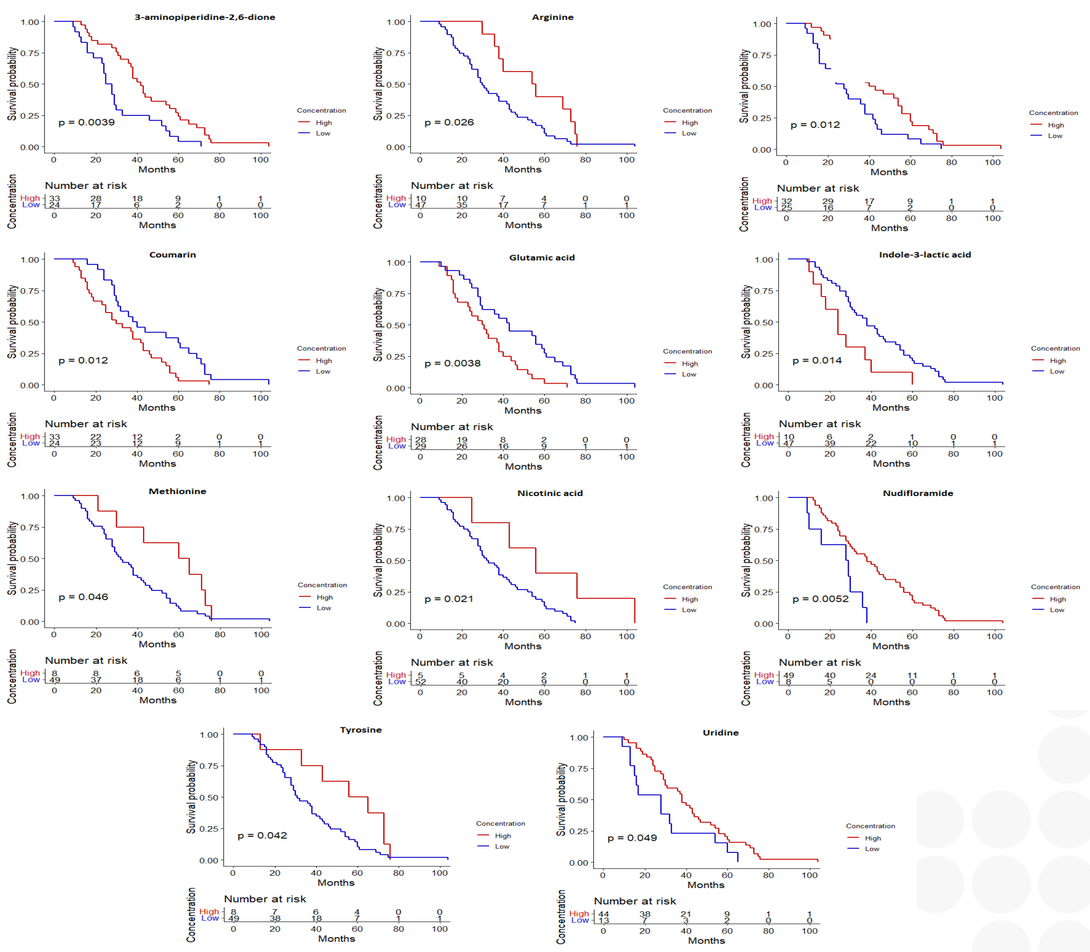


Figure 3. **Kaplan-Meir survival curves for ALS patients with neurotransmitter concentrations as a covariate.**

DISCUSSION

11 molecules could serve as prognostic markers. Lower circulating levels of 3-aminopiperidine-2,6-dione, arginine, cortisol, methionine, nicotinic acid, nudifloramide, tyrosine, and uridine are associated with poorer survival probability compared to higher circulating levels. In contrast, higher circulating levels of coumarin, glutamic acid, and indole-3-lactic acid are associated with poorer survival probability compared to lower circulating levels. Our data confirms the presence of altered neurochemical pathways in ALS patients that could be potentially used as prognostic markers or as targets for future therapies.

Acknowledgements: This study was (partially) funded by the Italian Ministry of University and Research program "Departments of Excellence 2023-2027", AGING Project – Department of Translational Medicine, Università del Piemonte Orientale.