Lung function

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Asociation between kynurenine metabolism in peripheral blood mononuclear cells and cognition in lung cancer patients undergoing chemotherapy

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Background. Cognitive impairement in lung cancer patients is observed before and after chemotherapy. It is associated with structural changes in brain white matter, not necessarily related to immune-mediated typical paraneoplastic neurological syndromes. Tumors, including lung cancer, are considered as sites of chronic sterile inflammation with the involvement of resident and monocyte-derived macrophages. Tryptofan metabolism via kynurenine pathway was found both in macrophages and microglial cells lines. The kynurenine pathway plays important role in immunosuppression, inflammation and neurodegeneration. L-Kynurenine (L-KYN) crosses blood-brain barrier and is further metabolised in the kynurenine pathway. Kynurenines can be produced in glial cells which express enzymes, like kynurenine aminotransferase (KAT) converting L-KYN to kynurenic acid, an inhibitor of glutamate neurotransmission. Thus, a link between kynurenine metabolism and cognition can be considered. Peripheral blood mononuclear cells (PBMC) can be considered as representative for metabolic changes in peripheral tisues during the course of lung cancer. The aim of the study was to evaluate kynurenine metabolism, expression of translocator protein 18 kDa (TSPO), which reflects microglia-line activation, G Protein-coupled Receptor (GPR35), a KYNA receptor and kynurenine aminotransferase II (KAT) in PBMC and serum L-KYN concentration in relation to cognition in lung cancer patients. Methods. The study included 221 patients (152 males aged 62,1 ± 7,8 and 69 females aged 62,6 ± 5,9 years. Among 221 patients 25 had small-cell lung cancer, 85 - adenocarcinoma, 62 - squamous cell carcinoma, 4 - large cell carcinoma, and 43 - NOS (not otherwise specified) and were hospitalized in Clinical Oncology with The Sub-department of Diurnal Chemotherapy Wielkopolska Center of Pulmonology and Thoracosurgery of Eugenia and Janusz Zeyland and Chair and Clinic of Oncology. Isolation of PBMC from venous blood was performed with the use of density gradient centrifugation. The expression of TSPO, GPR35, KAT in PBMC was evaluated by means of ELISA. Spectrofotometric method was applied for serum L-KYN and quinolinic acid concentration analyses. At baseline (time of lung cancer diagnosis) and after 6 months neurological examination, MiniMental State Examination (MMSE), Trail Making Test (TMT) A and B, and Hamilton scale evaluations were performed. Results. The expression of TSPO (translocator protein 18 kDa) in PBMCs was upregulated 6 months after chemotherapy (0; 0 – 229.06 ng /mg protein) compared to baseline (0; 0 - 166.3 ng /mg protein; P< 0.05) compared with total inhibition in patients without neurologcal (0; 0 - 0 pg / mg protein). We have found that down-regulation of TSPO expression in PBMC was associated with better MMSE score (29.00; 28.0–29.0; median, interquartile range) than in lung cancer patients with up-regulated TPSO (28.0; 26.0–28.7; P=0.016). TMT-A performance was more efficient in lung cancer patients with lowered TPSO (8.41±3.68s) compared to the subjects with up-regulated TPSO (12.92±7.30s; P=0.002). Moreover, TSPO expression in PBMC negatively correlated with MMSE score (Kendall's tau = -0.182; P=0.0178) and positively with TMT-A (Kendall's tau = 0.168; P=0.0309) evaluated at baseline. The stimulation of KAT expression in PBMC was associated with improved cognitive functions measured with MMSE 6 months after baseline (28.4±0.7) comparing to lung cancer patients with inhibited KAT (27.1±1.8). We noticed positive correlation between KAT and MMSE scoring 6 months after baseline (Kendall's tau= 0.308;

P=0.0234). No correlations between GPR35 expression in PBMC and cognitive measures were found in lung cancer patients. Serum L-KYN concentration correlated negatively with TMT-A evaluated 6 months after baseline (Kendall's tau= -0.586; P=0.0141). Conclusions. The effective metabolism of kynurenines in PBMC may play a protective role against cognitive decline during the course of lung cancer. The stimulation of microglia cel-line can be considered as an independent pathomechanism leading to cognitive impairment in lung cancer patients. The study was funded by the grant from National Science Center Poland No: UMO-2012/07/B/NZ7/04354