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Humoral response against glial derived antigens in Parkinson's disease

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HIGHLIGHTS

- Glial cells are involved in the neurodegeneration in Parkinson's disease.
- We checked whether glial cells degeneration induces immune response in Parkinson's disease.
- We checked whether this immune response against glial derived antigens changes over time.
- We provide the evidence for the presence of humoral response against glial derived antigens in PD.
- Immune system may be involved in the pathogenesis and progression of Parkinson's disease.

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ABSTRACT

To check whether glial cells have the ability to elicit adaptive immune response in Parkinson's disease and whether a change in this immune response can be observed over time. There is an increasing evidence that glial cells are involved in the neurodegenerative process in PD, in addition to neuronal structures. Measurement of autoantibodies against proteins of oligodendrocytes may serve as an indirect method to assess the level of glial cells activation or degeneration under in vivo conditions. Serum samples from 26 PD patients were collected twice, at baseline and after mean of 13 months. In addition, serum samples from 13 healthy controls matched for age and gender were assessed at one time point. IgG and IgM autoantibodies against myelin-oligodendrocyticglycoprotein (MOG), myelin basic protein (MBP), myelin-associated glycoprotein (MAG) and proteolipoprotein (PLP) were measured in all investigated subjects by a commercially available ELISA system (Mediagnost, Germany). In a group of PD significant decrease of IgG titers was observed for anti-MAG autoantibodies over the investigated time period ($p < 0.05$). For IgM antibodies, we observed statistically significant decrease in anti-MAG autoantibodies in the follow-up period ($p < 0.05$) and increase in anti-MBP and anti-PLP autoantibodies ($p < 0.05$). All antibody titers differed significantly between healthy control subjects and PD patients. Our study provides the evidence for the presence of humoral response against some glial derived antigens in PD. The increasing levels of anti MBP IgG and IgM might point to the value of this marker for monitoring disease progression.

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder next to Alzheimer's disease. The accumulation of α-synuclein in the cytoplasm of neurons classifies PD as an α-synucleinopathy. Nevertheless, there is an increasing evidence that in PD glial cells degeneration is involved in the neurodegenerative process in addition to neuronal structures. Some studies confirm that alpha-synuclein-positive inclusions are not only found in neurons, but also in oligodendrocytes and astrocytes of PD subjects [1,5,29] and number of alpha-synuclein-positive inclusions in these cells correlated positively with extent of neurodegeneration in the substantia nigra [29]. Additionally, glial cells in PD, contrary to other alpha-synucleinopathies, do not undergo reactive astrogliosis in the course of the disease progression, which is a neuroprotective mechanism [19]. The absence of reactive astrocytosis is indicative of a unique inflammatory process in PD [19,27]. Thus, it seems probable that not only neurons, but also glial cells in PD, which

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are involved in the degenerative process, have the ability to elicit adaptive immune response. It is known, for example, that autoantibodies against dopaminergic neurons are more common in PD than in healthy subjects [31]. Additionally, it is known that nigral degeneration may be accompanied by microglial inflammation [19,22,25]. Nevertheless, the relationship between the presence of pathological depositions of alpha-synuclein and inflammatory process in brain tissue of PD patients is not clear [6,9,25]. There is some evidence that activation of microglia by pathologic stimuli in the course of PD reduces their ability to degrade internalized α-synuclein aggregates. In PD, with progressive neuronal loss, increasing amounts of α-synuclein accumulate in the extracellular space and microglial dysfunction may be responsible for an inability to clear them effectively [12]. The measurement of autoantibodies against oligodendrocyte proteins serves, as an indirect method to assess the level of glial cells degeneration under in vivo conditions [15,21]. Although the involvement of glia in the progression of PD has been widely acknowledged, it is commonly thought that non-myelinating oligodendroglial cells are exclusively affected in PD, and only late in the disease process [8].

In demyelinating disorders, immune response against oligodendrocyte antigens was proposed as useful diagnostic indicator of disease progression [3]. Despite years of research, there is no one test or marker that can confirm the diagnosis of PD. Current diagnostic methods, based on medical history evaluation and neurological assessment fail to detect the disease before the onset of initial motor symptoms. Thus, the discovery of definitive blood biomarkers would be a major step toward the accurate diagnosis and the monitoring of the pathological process.

In this study, we hypothesized that in PD the immune response may not only be directed against antigens typically present in dopaminergic neurons but may be a more widespread process directed against antigens of glial cells. As there is no evidence for changes in oligodendroglia during the initial cellular stages of PD [8] we decided to investigate patients in advanced stages of the disease.

In order to reach the above goal, we prospectively assessed autoantibody levels: myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP), myelin-associated glycoprotein (MAG) and proteolipoprotein (PLP) in serum of patients suffering from PD and monitored their change in relation to clinical measures of disease progression over a period of 13 months. Such an approach might help to understand the role of glia-driven immune response in the pathogenesis of PD.

2. Materials and methods

26 PD patients in advanced clinical stage (Hoehn–Yahr scale 3–4) consecutively admitted to the Department of Neurology of Medical University of Lublin, Poland were enrolled. In addition, serum samples from 13 healthy controls matched for age and gender were assessed. Serum samples from PD patients were collected twice, at baseline (time-point #1) and after mean of 13 months follow-up (time-point #2). Serum samples from 13 healthy control subjects were assessed at one time point.

Blood were collected between 8:00 and 10:00 a.m., transferred to the lab on ice, centrifuged and serum was stored at −70 °C within 60 min thereafter.

The study was approved by the local ethics committee, and all study participants gave written informed consent for participation in the study.

IgG and IgM autoantibodies against myelin-oligodendrocyticglycoprotein (MOG), myelin basic protein (MBP), myelin-associated glycoprotein (MAG) and proteolipoprotein (PLP) were measured by a commercially available ELISA system according to the instructions of the manufacturer (Mediagnost, Germany). All analyses were performed in duplicate. The ELISA (E100) uses an internal standard pool serum for calculation of antibody titers and employing microplates coated with myelin-specific proteins purified from bovine brain. The autoantibody titer was calculated after the subtraction of nonspecific binding and blanks. The titers were estimated on the basis of calibration curve of autoantibody standards and expressed in Mediagnost Units per milliliter (MU/mL).

3. Statistical analysis

Antibodies titer differences between both evaluated time-points (study group) and control patients were estimated with the usage of ANOVA and Tukey–Kramer post hoc test. p-Value < 0.05 was considered statistically significant (two-sided). Statistical calculations were done with the usage of InStat GraphPad Software Inc., CA.

4. Results

Autoantibodies against MAG, MOG, MBP, PLP were detected in sera of all investigated subjects. Demographical, clinical and biochemical characteristics of the study population is shown in Table 1.

We observed statistically significant difference in autoantibodies titers between Parkinsonian patients and healthy control subjects for all assessed types of antibodies (both at time point 1 and at time point 2) ($p < 0.05$).

In the PD patients subgroup, significant decrease of titers was observed only for anti-MAG IgG autoantibodies over the investigated time period compared to baseline, for the rest of investigated IgG autoantibodies (anti-MOG, anti-MBP, anti-PLP) no statistically significant fluctuations were observed during follow-up (Table 1).

For IgM antibodies, we observed statistically significant decrease in anti-MAG autoantibodies in the follow-up period ($p < 0.05$) and increase in anti-MBP and anti-PLP autoantibodies ($p < 0.05$).

5. Discussion

The study provides the evidence for the presence of humoral response against certain glial derived antigens in PD. This seems interesting and important in the light of previous studies demonstrating the presence of antineuronal antibodies in patients with different movement disorders [17] and especially with idiopathic PD [30]. These results support the concept of immune response activated in the course of pathological process in PD. At the same time, the presence of small titers of autoantibodies in healthy control subjects, matched for age, can be explained by the mild microglial activation described in normal aging [23].

Our results are consistent with the previous study by Maetzler et al., which revealed the presence of humoral response against some antigens of glial origin in Lewy body dementias [15]. Among different dementive disorders, serum autoantibody levels against certain glial derived antigens (like MOG and MBP) turned out to be higher in Lewy body dementias compared to tau-associated dementias (like Alzheimer disease or Lewy body dementia), vascular dementia and healthy controls [15]. In addition, some studies confirmed that in different neurodegenerative disorder like PD or AD, serum autoantibodies may serve as highly specific and accurate biomarker [13,20].

Whether found antibodies reflect diffuse CNS injury or contribute to this injury is still unclear. For the antibodies to contribute to CNS pathology, they would have to gain access to the CNS through dysfunctional blood–brain barrier (BBB). The model