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In Vivo Measurement of Tau Depositions in Anti-IgLON5 Disease Using [18F]PI-2620 PET

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Abstract

Objectives

Anti-IgLON5 disease is a recently discovered neurologic disorder combining autoimmunity and neurodegeneration. Core manifestations include sleep disorders, bulbar symptoms, gait abnormalities, and cognitive dysfunction, but other presentations have been reported. Hallmarks are autoantibodies targeting the neuronal surface protein IgLON5, a strong human leukocyte antigen system Class II association, and brainstem and hypothalamus-dominant tau deposits. The purpose of this cohort study was to visualize tau deposition in vivo with the second-generation tau-PET tracer.

Methods

A cohort of 4 patients with anti-IgLON5 disease underwent a dynamic PET scan with [18F]PI-2620. One patient received a follow-up scan. Z-deviation maps and a 2-sample *t* test in comparison with healthy controls (n = 10) were performed. Antibody titers, neurofilament light chain, and disease duration were correlated with brainstem binding potentials.

Results

Patients demonstrated increased [18F]PI2620 tau binding potentials in the pons, dorsal medulla, and cerebellum. The longitudinal scan after 28 months showed an increase of tracer uptake in the medulla despite immunotherapy. Higher antibody titers and neurofilament light chain correlated with higher tracer retention.

Discussion

The results indicate that tau depositions in anti-IgLON5 disease can be visualized with [18F]PI-2620 and might correlate with the extent of disease. For validation, a larger longitudinal study is necessary.

Introduction

Anti-IgLON5 disease is a recently described disease with various symptoms such as parasomnia, sleep apnea, and stridor.[1] It displays features of an autoimmune and neurodegenerative disorder: The presence of autoantibodies against the neuronal surface protein IgLON5 and the association with HLA-DRB1*10:01 and HLA-DQB1*05:01 alleles of the human leukocyte antigen system are hallmarks of an autoimmune etiology. Tau deposits—especially in the hypothalamus and tegmentum of the brainstem[2]—point toward neurodegenerative mechanisms.

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The diagnosis of anti-IgLON5 disease is made by detection of IgLON5 autoantibodies[3] or postmortem on neuropathologic criteria.[2] The only way to measure tau depositions in anti-IgLON5 disease antemortem is molecular imaging. [18F]PI2620 is a second-generation tau-PET tracer with low off-target binding.[4] Only 1 case of tau-PET imaging has been reported in anti-IgLON5 disease. The first-generation tau tracer [18F]THK-5351 with known unspecific binding patterns[5] showed increased binding in the cerebellum and brainstem.[6]

The objective of this exploratory study was to examine whether [18F]PI2620 is able to detect cerebral tau deposits in patients with anti-IgLON5 disease in vivo.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Patients had been included in the German Network for Research on Autoimmune Encephalitis (GENERATE). Initial institutional review board (IRB) approval was given by the ethical advisory board of the University of Luebeck, Germany (reference number: 13-162), and GENERATE was approved by IRBs of all actively recruiting centers. The study was performed according to the Declaration of Helsinki. Written informed consent was given before enrollment in the registry.

Cohort

Four patients with the diagnosis of anti-IgLON5 disease received [18F]PI-2620 PET at the University Hospital of Cologne. An established healthy control data set was used.[4] Clinical information is given below.

Image Acquisition and Preprocessing

All patients underwent a 90-minute dynamic PET scan with [18F]PI2620. Patient 2 returned for a follow-up after 28 months. PET was performed on a Siemens mCT PET scanner (Siemens, Erlangen, Germany). SPM12 was used for preprocessing. Binding potential maps were calculated with the Simplified Reference Tissue Model 2 in QModeling.[7,8] Regions of interest (ROIs) were chosen according to neuropathologic criteria.[2] The bilateral paracentral gyrus was chosen as the reference region because a 2-sample test between patients and healthy controls using SPM12 showed relatively higher tracer binding in controls.[9]

Voxel-Wise and ROI-Based Statistical Analyses

Time from symptom onset until PET was calculated. A 2-sample t test and χ^2 test were performed for differences in age and sex. Normal distribution of clinical and ROI data was checked by using the Shapiro-Wilks test.

We calculated individual z-deviation maps (patients > healthy controls) using MATLAB (R2017b). For patient 2, we calculated the percentage ΔImage of the binding potential images:

$$\Delta\text{Image} = \left(\text{Image}_{\text{Follow-up}} - \text{Image}_{\text{Baseline}} \Big/ \text{Image}_{\text{Baseline}}\right) \times 100 \quad (1)$$

A pseudo t test was calculated between patients and controls in Statistical NonParametric Mapping (SnPM).[10] For regions with an a priori hypothesis according to the neuropathologic criteria, we accepted $p < 0.001$ uncorrected because of the small sample size.

In the resulting region, we extracted the mean binding potential with REX.[11] Using SPSS (version: 28.0.1.0), we performed Pearson correlations with binding potential and antibody titer and neurofilament light chain (NfL) in serum, disease duration, and untreated disease duration.

We performed a ROI analysis of the brainstem using the BrainstemNavigator[12] including the following subregions: vestibular nuclei complex, pedunculopontine nuclei, periaqueductal gray, dorsal raphe, laterodorsal tegmental nuclei, and viscerosensory motor nuclei complex.

Data Availability

Data will be made available on reasonable request.

Results

Characterization of the Cohort

The cohort consisted of 3 male patients and 1 female patient. The mean age was 66 years (range: 55–81 years).

Patient 1

The patient had vertical gaze palsy, dysphagia, dysarthria, gait instability, and day-time sleepiness for 5 years. Antibodies were 1:3,200 in serum and 1:3,200 in CSF. The haplotypes present were HLA-DRB*10:01 and HLA-DQB1*05:01. Immunosuppression (2 years after symptom onset) included IV immunoglobulins (IVIgs) monthly and azathioprine. There was a decrease in antibody titer in serum (1:1,000). Dysphagia and dysarthria improved under immunotherapy.

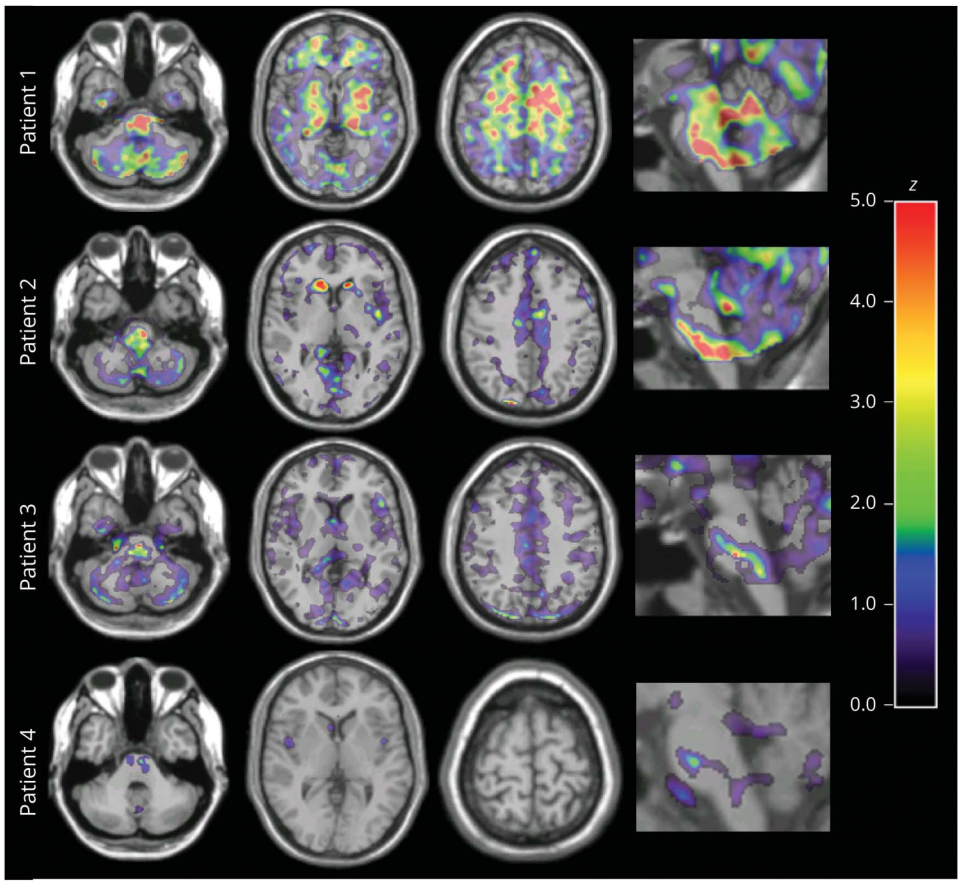
Patient 2

Patient 2 had diplopia, square wave jerks, fasciculations, postural arm tremor, gait instability, and sleep apnea for 1 year. Antibodies were 1:1,000 in serum and 1:1,000 in CSF. The HLA-DRB*10:01 haplotype was present. Immunotherapy (6 months after symptom onset) included 2 high-dose methylprednisolone pulses (1 g for 5 days), followed by oral prednisolone, IVIg, and azathioprine. There was improvement of double visions. Antibodies in follow-up were 1:1,000 in serum and 1:10 in CSF.

Patient 3

This patient had diplopia, square wave jerks, cognitive decline, and gait disturbance for 4 years. Polysomnography revealed sleep apnea. Antibodies were 1:320 in serum and 1:100 in CSF. HLA-DRB*10:01 and HLA-DQB1*05:01 haplotypes were found. Immunotherapy (8 months after symptom onset) included methylprednisolone pulse therapy and rituximab. Antibodies in follow-up were between 1:3,200 and 1:10,000 in serum. The clinical course was unchanged.

Figure 1 Individual Z-Deviation Maps of [18F]PI-2620 Binding Potential

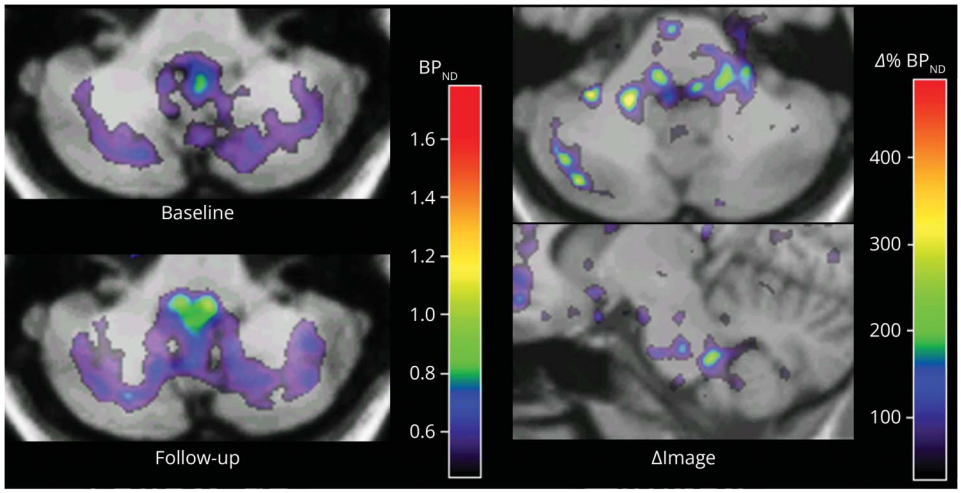


Contrasts: patients > healthy controls.

Patient 4

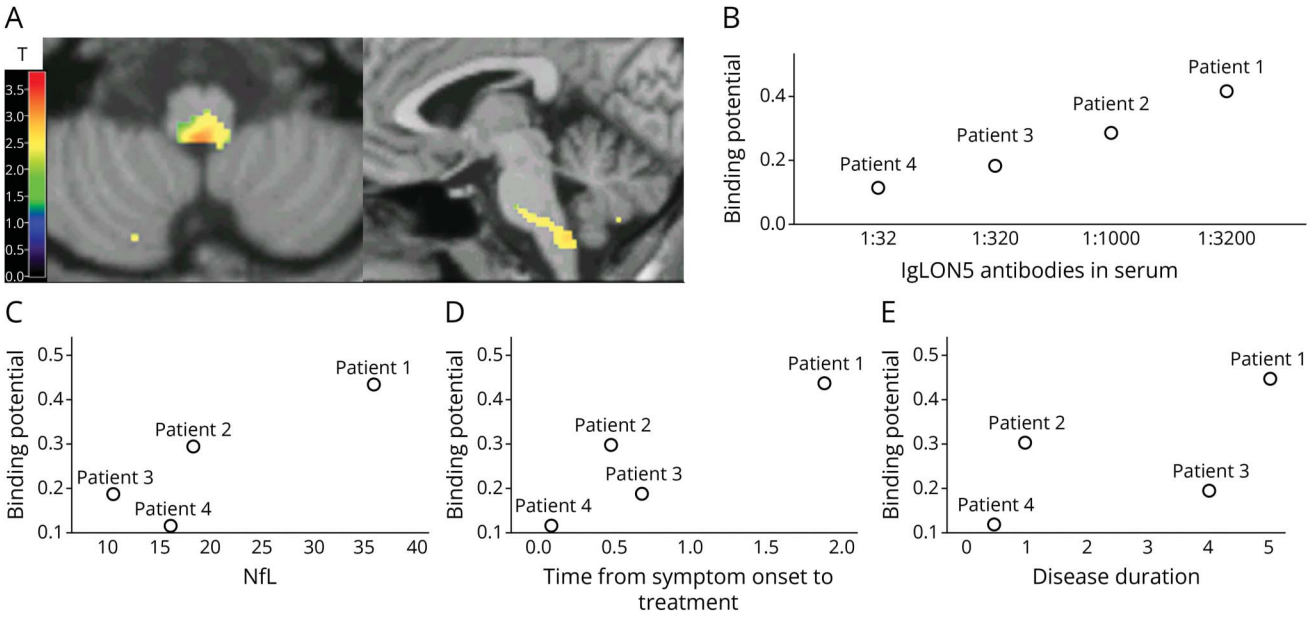
The patient had right fourth cranial nerve palsy for 6 months. Antibodies were 1:32 in serum; no antibodies were found in CSF. The HLA-DQB1*05:01 haplotype was present. Immunotherapy (1 month after symptom onset) included methylprednisolone pulse and IVIgs. Antibodies in follow-up were 1:

Figure 2 Longitudinal Tau Imaging



Voxel-wise binding potential map of patient 2 at baseline and after 28 months (left side). The ΔImage shows a regional increase of tau deposition over time in the dorsal medulla oblongata and cerebellum in percent. $\Delta Image = (Image_{Follow\text{-}up} - Image_{Baseline}/Image_{Baseline}) \times 100$ (right side).

Figure 3 The Link Between Tau-PET and Clinical Data



(A) Two-sample *t* test between the voxel-wise binding potential maps of patients and healthy controls in SnPM. Contrast: patients > healthy controls. For illustratory purposes, the threshold was set to $p < 0.05$ uncorrected. (B–E) Scatterplots of mean binding potential in the brainstem clusters of the 2-sample *t* test and IgLON5 antibodies in serum (B), neurofilament light chain (NfL) in the serum (pg/mL) (C), time from symptom onset to treatment initiation in years (D), and disease duration in years (E). A figure with age-corrected z-scores of NfL and binding potential is in eFigure 1 (links.lww.com/WNL/D169).[15]

100 in serum. The patient developed severe sleep apnea and vertical gaze palsy.

Healthy Controls

There were 6 male and 4 female healthy controls. Their mean age was 59 years (range 50–75 years). No significant differences were observed between patients and controls concerning age and biological sex in the 2-sample *t* test ($p = 0.277$) and χ^2 test ($p = 0.597$).

Imaging Results

Voxel-Wise

Individual z-deviation maps are presented in Figure 1. All 3 patients with an extended clinical phenotype showed a brainstem-dominant but widespread uptake. Patient 4, with a more restricted clinical phenotype, demonstrated only slight uptake in the brainstem. Visual inspection of the follow-up scan revealed an increase in tau depositions in the medulla (Figure 2).

Patients had higher binding potentials than controls in the dorsal medulla (x = 2, y = −40, z = −56, pseudo-$T = 3.02$), pons (x = −4, y = −22, z = −42, pseudo-$T = 3.17$), and cerebellum (x = −34, y = −82, z = −44, pseudo-$T = 3.18$) (Figure 3A). There was a positive correlation between binding potential and IgLON5 antibody titers in serum ($R = 0.96$, $p = 0.04$) (Figure 3B) and a trend of significant correlation between binding potential and NfL ($R = 0.87$, $p = 0.13$) (Figure 3C, see also eFigure 1, links.lww.com/WNL/D169). There was no correlation between binding potential and duration from symptom onset until treatment initiation and disease duration (Figure 3, D and E).

ROI-Based

Two-sample *t* test revealed that patients had a higher binding potential than controls in the viscerosensory motor nuclei complex ($p = 0.019$) consolidated by a strong effect size ($g = 1.294$). No other significant difference between patients and controls was found.

Discussion

We could demonstrate that in vivo tau-imaging using [18F]PI2620-PET corresponds to postmortem tau depositions of a previous study and extent of disease in a small cohort of patients with anti-IgLON5 disease.[2] The ROI analysis revealed tau deposits in the viscerosensory motor nuclei complex, lesions of which have been associated with disruptions of sleep and alertness, autonomic dysregulation, vertigo, and impaired control of eye movements and gait.[13]

We observed 2 associations with brainstem tracer uptake: Severity of clinical symptoms was associated with tau deposition on a descriptive level. The antibody titer in serum, which has been observed to correlate with limited/extensive disease,[3] showed a strong positive association with tracer uptake in the brainstem. This was emphasized by a strong correlation between NfL and tracer uptake. The follow-up scan available in patient 2 showed an increase in tau depositions in the medulla although symptoms and the antibody titer improved. This observation of tau deposition being a late aspect of disease manifestation possibly secondary to autoantibody-induced tau hyperphosphorylation is in line with a recent neuropathologic study observing lack of tau

deposition in an early disease stage.[14] This might explain the dissociation of clinical course and imaging.

Our report is limited by the small sample size and the exploratory nature of the analysis. We reported results with liberal statistical thresholds. The PET results were not confirmed by neuropathology. Ongoing data collection may overcome these limitations.

We infer that [18F]PI-2620 is able to detect tau depositions in anti-IgLON5 disease and likely reflects extent of manifest tissue pathology.

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Disclosure

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Continued

Appendix *(continued)*

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