In Vivo Measurement of Tau Depositions in Anti-IgLON5 Disease Using $^{18}$F-PI-2620 PET

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Contributions:
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Thilo Van Eimeren: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
3

Table Count:
0

Search Terms:
[ 132 ] Autoimmune diseases, [ 244 ] All Sleep Disorders, [ 122 ] PET

Acknowledgment:

Study Funding:
Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) (Project No. 413543196). GENERATE is supported by the German Ministry of Education and Research (BMBF, 01GM1908 and 01GM2208).

Disclosure:
H. Theis was supported by the program for rotation positions/Faculty of Medicine/University of Cologne and by the Cologne Clinician Scientist Program (CCSP) / Faculty of Medicine / University of Cologne. G.N. Bischof reports no disclosures relevant to the manuscript. N. Brüggemann received honoraria from Abbott, Abbvie, Biogen, Biomarin, Bridgebio, Centogene and Zambon. Dr. Brüggemann was supported by the DFG (BR/4328.2-1, GRK1957), the Michael J Fox Foundation, and the EU Joint Programme – Neurodegenerative Disease Research (JPND). J. Dargvainiene reports no disclosures relevant to the manuscript. A. Drzezga reports no disclosures relevant to the manuscript. T. Grüter reports no disclosures relevant to the manuscript. J. Lewerenz received speaker fees or travel compensation from the International Parkinson and Movement Disorder Society and the Cure Huntington's Disease Initiative (CHDI). His institution has been reimbursed for his role as a principal investigator in trials for UCB and CHDI. His research is funded by the European Huntington's Disease Initiative and Ministry for Education and Research Baden-Wuerttemberg, outside the submitted work, and the German Federal Ministry of Education and Research (BMBF). He works for an academic institution, which also offers commercial antibody testing. F. Leyboldt reports having received speaker's honoraria and travel support from Grifols, Roche, Alexion and Biogen. He is part of an advisory board to Roche, Biogen and works for an academic institution offering commercial antibody testing. B. Neumaier reports no disclosures relevant to the manuscript. K.P. Wandinger reports no disclosures relevant to the manuscript. I. Ayzenberg reports no disclosures relevant to the manuscript. T. van Eimeren received honoraria and speaker fees from Orion Pharma, Lundbeck Pharma, Athenenum, and the International Movement Disorders Society. He receives a stipend for consultancy work from the Lundbeck Foundation. Multiple unrelated research projects are currently supported by the German Research Foundation.

Preprint DOI:

Received Date:
2023-06-01

Accepted Date:
2023-08-22
Abstract

Background and Objective:

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

Methods: A cohort of four patients with anti-IgLON5 disease underwent a dynamic PET scan with $^{18}$F-PI-2620. One patient received a follow-up scan. Z-deviation maps and a two-sample t-test in comparison to healthy controls (n=10) were performed. Antibody titers, neurofilament light chain and disease duration were correlated with brainstem binding potentials.

Results: Patients demonstrated increased $^{18}$F-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 $^{18}$F-PI-2620 and might correlate with 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 apnoea, and stridor\(^1\). It displays features of an autoimmune and a 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 (HLA) are hallmarks of an autoimmune etiology. Tau deposits – especially in the hypothalamus and tegmentum of the brainstem\(^2\) - point towards neurodegenerative mechanisms.

The diagnosis of anti-IgLON5 disease is made by detection of IgLON5 autoantibodies\(^3\) or post-mortem upon neuropathological criteria\(^2\). The only way to measure tau depositions in anti-IgLON5 disease ante-mortem is molecular imaging. \(^{18}\)F-PI2620 is a second-generation tau-PET tracer with low off-target binding\(^4\). Only one case of tau-PET imaging has been reported in anti-IgLON5 disease. The first-generation tau tracer \(^{18}\)F-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 \(^{18}\)F-PI2620 is able to detect cerebral tau deposits in patients with anti-IgLON5 disease in vivo.

Methods

Standard Protocol Approvals:

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 \(^{18}\)F-PI-2620 PET at the University Hospital of Cologne. An established healthy control dataset was used\(^4\). Clinical information is given below.
**Image Acquisition and Preprocessing**

All patients underwent a 90-minute dynamic PET scan with $^{18}$F-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 neuropathological criteria$^2$. The bilateral paracentral gyrus was chosen as reference region, since a two-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 two-sample $t$-test and a chi-squared test were performed for differences in age and sex. Normal distribution of clinical and ROI data was checked by using Shapiro-Wilks-Test.

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

$$\Delta \text{Image} = \left( \frac{\text{Image}_{\text{Follow-up}} - \text{Image}_{\text{Baseline}}}{\text{Image}_{\text{Baseline}}} \right) \times 100$$

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 neuropathological criteria, we accepted $p<0.001$ uncorrected due to 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 grey, dorsal raphe, laterodorsal tegmental nuclei and viscero-sensory motor nuclei complex.

**Data availability:**

Data will be made available on reasonable request.
Results

Characterization of the cohort (3 males and 1 female, mean age: 66, range: 55-81)

Patient 1: Vertical gaze palsy, dysphagia, dysarthria, gait instability and day-time sleepiness for five years. Antibodies: 1:3200 serum, 1:3200 CSF. Haplotype: HLA-DRB*10:01 and HLA-DQB1*05:01. Immunosuppression (2 years after symptom onset): IVIGs monthly and azathioprine. Decrease in antibody titer in serum (1:1000). Dysphagia and dysarthria improved under immunotherapy.

Patient 2: Diplopia, square wave jerks, fasciculations, postural arm tremor, gait instability and sleep apnea for one year. Antibodies: 1:1000 serum, 1:1000 CSF. Haplotype: HLA-DRB*10:01. Immunotherapy (6 months after symptom onset): 2 high-dose methylprednisolone pulses (1g for 5 days) followed by oral prednisolone, IVIG and azathioprine. Improvement of double visions. Antibodies in follow-up: 1:1000 serum, 1:10 CSF.

Patient 3: Diplopia, square wave jerks, cognitive decline, and gait disturbance for four years. Polysomnography revealed sleep apnea. Antibodies: 1:320 in serum, 1:100 CSF. Haplotype: HLA-DRB*10:01 and HLA-DQB1*05:01. Immunotherapy (8 months after symptom onset): methylprednisolone pulse therapy, rituximab. Antibodies in follow-up: between 1:3200 and 1:10000 in serum. Clinical course was unchanged.

Patient 4: Right fourth cranial nerve palsy for six months. Antibodies: 1:32 serum, no antibodies in CSF. Haplotype: HLA-DQB1*05:01. Immunotherapy (1 month after symptom onset): methylprednisolone pulse and IVIGs. Antibodies in follow-up: 1:100 in serum. The patient developed severe sleep apnea and vertical gaze palsy.

Healthy controls: Six males and 4 females. Mean age: 59 years (range 50-75 years). No significant differences between patients and controls concerning age and biological sex in two-sample t-test ($p=0.277$) and chi-squared test ($p=0.597$).
Imaging Results

Voxel-wise:
Individual z-deviation maps are presented in Figure 1. All three patients with an extended clinical phenotype showed a brainstem-dominant but widespread uptake. Patient 4, with 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 (Fig. 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 the serum (R=0.96, p=0.04) (Fig. 3B) and a trend significant correlation between binding potential and NfL (R=0.87, p=0.13) (Fig. 3C, see also eFigure 1). There was no correlation between binding potential and disease duration and duration from symptom onset until treatment initiation (Fig. 3D, 3E).

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 $^{18}$F-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 two 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 even though 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 neuropathological study observing lack of tau deposition in an early disease stage. This might explain the dissociation of clinical course and imaging.

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

**Conclusions**
We infer that $^{18}$F-PI-2620 is able to detect tau depositions in anti-IgLON5 disease and likely reflects extent of manifest tissue pathology.

WNL-2023-002287_efig1 --- [http://links.lww.com/WNL/D169](http://links.lww.com/WNL/D169)
References:


Figure legends

Figure 1: Individual z-deviation maps of PI-2620 binding potential. Contrasts: patient > healthy controls.

Figure 2: 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 the cerebellum in percent. ΔImage=(ImageFollow-up−ImageBaseline/ ImageBaseline)×100 (right side)
Figure 3: 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, C, D: Scatterplots of mean binding potential in the brainstem clusters of the two-sample t-test and IgLON5 antibodies in serum (B), NfL in the serum (pg/mL) (C), time from symptom onset to treatment initiation in years (D) and disease duration (E). A figure with age-corrected z-scores of NfL and binding potential is in the supplemental material (eFigure 1).
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Neurology published online October 25, 2023
DOI 10.1212/WNL.0000000000207870

This information is current as of October 25, 2023