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NMDA Receptor Antibodies and Neuropsychiatric Symptoms in Parkinson's Disease

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Abstract

Background: NMDA receptor (NMDAR) encephalitis is an autoantibody-mediated neurological syndrome with prominent cognitive and other neuropsychiatric symptoms (NPS). NMDAR antibodies (ab) are also detected outside encephalitis but the clinical relevance of this is unknown.

Method: Plasma from 108 patients with Parkinson's disease (PD) and 89 healthy controls (HC) was screened at baseline for IgA, IgM and IgG NMDAR ab, plasma p-tau181 and the neuro-axonal injury marker neurofilament light (NfL). Clinical assessment of PD patients at baseline included cognition (MMSE) and other NPS (Hospital Anxiety Depression Score and Non-Motor Symptom Scale), a subgroup (n=61) were followed up annually for up to 6 years.

Results: 10 (9.3%) PD patients tested positive for NMDAR ab (5 IgA, 6 IgM and 0 IgG) and 3 (3%) HC had IgM NMDAR ab; IgA NMDAR ab were significantly more common in PD patients versus HC (X^2=4.23, p=0.04). No association with age, gender or duration of disease was seen with NMDAR ab positivity. In the subgroup followed longitudinally, Ab positive (ab+) PD patients had significantly greater decline in annual MMSE score when years of education, age, duration of disease, plasma p-tau181, NfL and length of follow up were adjusted for (adjusted R^2=0.26, p=0.01). Other NPS were not associated with ab status and no association was seen between NMDAR ab and p-tau181 or NfL.

Conclusions: NMDAR ab were associated with greater cognitive impairment over time in PD patients, independent of the other pathological biomarkers measured, suggesting these antibodies could contribute to the cognitive decline in PD.

Introduction

Antibodies to neuronal surface antigens such as the NMDA receptor (NMDAR) cause an autoimmune encephalitis characterised by cognitive dysfunction, psychiatric symptoms, seizures and movement disorder [1]. While it is the NMDAR antibody (ab) IgG isotype which mediates encephalitis, NMDAR ab particularly of IgA and IgM isotype, are also detected in patient populations in the absence of encephalitis. While NMDAR ab of all isotypes have been shown to have pathogenic potential with impaired glutamatergic signalling likely due to internalisation of NMDAR at the synapse [2], the clinical significance of NMDAR ab outside the context of encephalitis is currently unclear. However, in a number of clinical populations including patients with cancer [3], psychosis spectrum disorders [4], stroke [5] and post-viral encephalitis [6], IgA and IgM NMDAR ab have been associated with cognitive impairment. In psychosis spectrum disorders and, more recently stroke, there is also some evidence to suggest NMDAR ab are associated with neuropsychiatric symptoms such as psychosis and depression [4, 7, 8]. An association has also been reported between NMDAR ab and psychotic symptoms in Alzheimer's disease (AD) but this has not been consistently replicated [9, 10].

NMDAR ab are found in dementia populations, particularly where the dementia subtype is atypical or unclassified, and the cognitive impairment is often reversible with immunotherapy [8, 11]. However, neuronal antibodies, particularly to the NMDAR, are also found in well-phenotyped, classical presentations of neurodegenerative disease, though it is not clear how this relates to the cognitive and other neuropsychiatric symptoms [12]. This is an important question to address given the potential reversibility of any antibody-mediated changes for symptoms which currently have few effective treatment options.

Neuropsychiatric symptoms and cognitive impairment are common in PD with more than 80% of patients developing dementia 20 years post-diagnosis [13]. The time course behind this is highly variable and likely reflects the contribution of many factors such as α-synuclein, phosphorylated tau and beta-amyloid [14]. The role of inflammation is also increasingly recognised in PD, including a possible role for humoral immunity influencing clinical phenotype [15]. However, studies looking at the prevalence and clinical relevance of NMDAR ab in Lewy body disease have produced conflicting results; increased frequencies of serum IgA/IgM NMDAR ab have been found in Lewy body dementias (dementia with Lewy bodies and PD dementia) [10] while another study found no association with IgA antibodies and the cognitive impairment in PD, although the cognitive dysfunction exhibited by the included patients in this study was modest [16].

Where NMDAR ab do occur in neurodegenerative disease, the site of autoantibody production is not clear. In autoimmune encephalitis, it is likely that ongoing peripheral germinal centre reactions generate antigen-specific plasma B cells, which differentiate and access the CNS to produce pathogenic IgG [17]. In neurodegenerative disease, it may be that the accelerated neuronal cell death and apoptosis leads to production of these antibodies. If NMDAR ab were produced following neuronal death, seropositivity might be expected to associate with higher plasma levels of neurofilament light (NfL), a marker of neuroaxonal injury [18] and p-tau181, a marker of phosphorylated tau [19]. In acute NMDAR ab encephalitis CSF NfL and tau have been reported to be markedly elevated, decreasing with treatment [20, 21] but these biomarkers have not been examined in association with neuronal antibodies outside encephalitis. Increased concentration of plasma NfL and p-tau181 is associated with faster cognitive decline in Lewy body dementias [22, 23] and so in measuring these biomarkers in association with NMDAR ab we also hope to be able to delineate any

potential influence on the cognitive and neuropsychiatric symptoms in PD.

Using a well-characterised prospective cohort of PD patients, we aimed to address 3 questions: 1) to quantify the frequency of IgA, IgM, and IgG NMDAR ab in PD relative to healthy controls 2) to explore association between NMDAR ab positivity and the cognitive and neuropsychiatric symptoms in PD both at baseline and longitudinally and 3) to investigate the relationship between NMDAR ab and plasma p-tau181 and NfL.

Methods

Patient cohort

Baseline plasma samples were taken from 108 patients with a clinical diagnosis of idiopathic PD from the King's College Hospital centre of the Non-motor International Longitudinal Study (NILS) and 89 healthy controls (HC). The NILS is a prospective cohort study designed to assess outcomes from non-motor symptoms in PD over time, patients are initially assessed at baseline with plasma samples taken and clinical measures administered. Patients are then assessed annually with clinical measures for up to 6 years after inclusion. All included patients had a diagnosis of PD made by movement disorder specialist clinicians according to internationally recognised criteria [24]. Exclusion criteria included atypical parkinsonism, age of PD onset < 21, insufficient clinical information or archived plasma for analysis available. The NILS study was authorised by local ethics committees (NRES South East London REC, 10084, 10/H0808/141). All patients gave written consent prior to study procedures and all patient data were anonymised and coded.

Plasma samples from 89 consented HC were retrieved from archives in the South London and Maudsley Biomedical Research Centre (BRC), samples were age- and sex-matched at the group level to the extent possible from the available archived samples.

Clinical data

Data extracted for PD patients from the NILS database included sex, age, PD onset (years), years of education, Hoehn and Yahr stage for PD progression [25], Scales for Outcomes in Parkinson's Disease (SCOPA-motor) [26], Non-Motor Symptom Scale (NMSS) [27], Hospital Anxiety and Depression Scale (HADS) [28] and Mini Mental State Examination (MMSE) scores [29]. Scales were administered by research clinicians. Psychotic symptoms were extracted from the hallucination and delusion items on the NMSS and patients were considered to meet criteria for psychosis if scoring ≥ 1 where frequency and severity were combined.

Plasma NMDAR antibody

All plasma samples were tested for NMDAR ab using fixed cell-based assays (CBAs) and testers were blinded to all clinical information. Samples were stored at −80°C until assayed. IgA, IgM and IgG NMDAR ab were detected with a recombinant cell line transfected with an expression construct for the reactive receptor subunit NR1 utilising indirect immunofluorescence (Euroimmun NMDAR kit) as described previously [30]. Transfected human embryonic kidney 293 cells were incubated with plasma dilution 1:10 from each patient; FITC conjugated secondary antibodies (IgG, IgA and IgM) were then added and antibody binding was measured by immunofluorescence.

Plasma NfL concentration

Plasma NfL concentration was measured using the commercially available NF-Light kit on a Single molecule array (Simoa) HD-1 Analzyer in n=143 samples (PD n=105, HC n=38) at UK DRI Fluid Biomarker Laboratory, London, UK in one round of experiments using one

batch of reagents. Testers were blinded to samples and 91% (n = 130) were measured in duplicate (insufficient sample available for n=13; 6PD, 7 HC). Intra-assay coefficients of variation were <5%. The limit of detection (LOD) was 0.038 pg/mL and the lower limit of quantification (LLOQ) was 0.174 pg/mL.

Plasma p-tau181 concentration

Plasma p-tau was measured for 104 PD samples at King's College London using the commercially available Simoa® pTau-181 V2 Advantage Kit (Quanterix; 103714). Plasma was diluted 1:4 and read on the HD-1 analyser. Data acquisition spanned 5 analytical runs, the lower limit of quantification (LLOQ) for this assay was 0.127 pg/mL and the coefficient variation (CV) for inter and intra-assay variability was 7.51% and 7.69% respectively.

Statistical analysis

HC and PD patients were compared for age, gender, antibody status and NfL concentration. Seropositive and seronegative PD patients were compared for neuropsychiatric symptoms, cognitive outcomes and functional disability both at baseline and during follow up. Continuous variables were compared using the independent t-tests or Mann-Whitney U-tests, distribution dependent. Categorical data were analyzed with the Chi squared or Fisher's exact tests.

To assess the longitudinal impact of NMDAR ab, annual decline in MMSE was calculated from the decline in MMSE score over the follow up period. Linear regression was performed for annual decline in MMSE with NMDAR antibody status (positive or negative) and age, sex, years of education, duration of follow up, duration of disease (months), p-tau181 and NfL as covariates. Cognitive impairment was also separately classified dichotomously;

patients with MMSE<26 were classified as cognitively impaired.

To achieve normality, NfL concentration and p-tau181 were log transformed. Linear regression was used to analyse log NfL and log p-tau181 concentration with NMDAR ab status with age as a covariate.

Significance threshold was set to $p < 0.05$, and where applicable values are given for two-tailed tests. Significance values are uncorrected for multiple comparisons due to the exploratory nature of the analyses. Statistical tests were carried out with Stata version 16.0.

Results

Participants

108 PD patients (25% female; mean age 63.7±11.9) were included and 89 HC (34% female; mean age 54.2±17.0). HC patients were significantly younger than PD patients ($p < 0.001$). *Table 1.* Mean Hoehn and Yahr stage (H&Y) for PD patients was 2.34+0.76. Duration with PD at baseline was highly variable with a median of 6.8 years (range 1 – 32).

61 (56%) PD patients (28% female, mean age 63.3±11.6) were followed longitudinally for mean 3.69 years ±1.73 (median 3.99, range 0.71-6.61 years). Baseline mean MMSE score was 28.8±2.4, declining by mean 0.60±1.24 points annually during follow up.

Frequency of plasma NMDAR ab+ in PD v HC

10 (9.3%) PD patients tested positive for NMDAR ab; 5 IgA, 6 IgM and 0 IgG NMDAR ab. 3 HC (3%) tested positive for NMDAR ab, all with an IgM isotype antibody. *Figure 1.* IgA NMDAR ab were significantly more common in PD patients ($X^2=4.23$, $p=0.04$); no IgA

NMDAR ab were found in HC. (*Figure 1C).* There was no association between NMDAR ab positivity and age (mean age Ab+ 61.05, Ab- 59.3, t(195) = -0.41, p = 0.68).

No demographic differences with NMDAR ab positivity within PD group

No difference in age t(106)=0.39, p=0.69), gender (X^2 =0.15, p=0.70), age of PD onset (t(106)=0.51, p=0.61) or duration of follow up (t(59)=-0.78, p=0.44) was seen with NMDAR ab positivity in PD patients. There was also no difference in motor symptoms (t(81)=0.13, p=0.89) or degree of disease progression (H&Y) (*U*=0.12, p=0.93) based on antibody status. *Table 2.*

Cognitive associations of NMDAR ab positivity in PD

At baseline, there was no difference in MMSE score based on antibody status, (*U* = 0.29, p = 0.77). However, antibody status was a significant predictor of annual decline in MMSE in linear regression adjusted for age, sex, years of education, p-tau181, NfL, duration with PD and duration of follow up (adjusted R^2=0.26, p = 0.01). The mean annual decline in MMSE was 1.36±2.55 for ab+ patients and 0.50±0.96 for ab- patients. *Figure 2.* During the follow up period of the cohort study, 13 PD patients (21%) showed evidence of cognitive impairment (MMSE<26); of these 31% (n=4) were seropositive for NMDAR ab. For those followed longitudinally 57% (n=4) of ab+ patients showed evidence of cognitive impairment at some time point in the course of the study versus 17% (n=9) of ab- PD patients, X^2= 6.05, p = 0.014. *Table 3.*

Neuropsychiatric outcomes with NMDAR ab positivity

During the course of the study, 37 (35%) PD patients reported psychotic symptoms (22 at baseline and 15 emergent psychosis in the follow up period). There was no relationship

between psychotic symptoms and NMDAR antibody status (ab+ 42.9% (n=3) v ab- 54.0% (n=34), X^2=0.31 p = 0.58).

Baseline HADS showed high morbidity of depression and anxiety across PD patients (mean HADS 10.4±7.41). Baseline HADS was not significantly different across ab+ and ab- PD patients (*U*=0.55, p = 0.59). The mean change in HADS score during follow up was an increase of 6.56±6.34 and this was not significantly different based on ab positivity (*U*=-0.93, p = 0.35).

Plasma NfL and p-tau181 concentration with NMDAR antibody positivity

Mean NfL concentration across all samples was 25.3pg/mL ± 17.4. NfL concentration was lower in HC (mean 23.5 ±20.2pg/mL) than in PD samples (mean 25.9±16.3pg/mL), but the difference was not significant (logNfL t(141) = -0.74, p = 0.46). Within PD patients, in age-adjusted linear regression there was no association between NfL concentration and ab status (R^2=0.17, p = 0.92). In PD patients mean plasma p-tau181 was 2.32±1.36pg/ml. There was no association between plasma p-tau181 and antibody status in linear regression adjusted for age (adjusted R^2=0.10, p = 0.32).

Discussion

In one of the first studies to investigate the possible longitudinal implications of NMDAR ab in neurodegenerative disease, IgA NMDAR antibodies were found at increased frequencies in PD patients, with seropositive patients showing significantly greater cognitive impairment over time. Over half (57%) of all seropositive patients with PD were cognitively impaired during the study while only 17% of seronegative patients showed evidence of cognitive

impairment. Seropositive patients showed significantly greater annual cognitive decline irrespective of p-tau181, NfL concentration and other clinical and demographic variables. This suggests that any antibody-associated cognitive impairment occurs independent of these co-existing neurodegenerative processes.

NMDAR antibody isotype

When NMDAR ab are detected outside encephalitis they are primarily of the IgA and IgM isotype. Consistent with previous studies we found exclusively IgA and IgM antibodies, with IgA NMDAR ab only found in PD patients rather than HC. There is some disagreement as to the clinical relevance of IgA and IgM ab, while in vitro, all NMDAR ab isotypes have been shown to have the potential to cause receptor internalisation and dysfunction to glutamatergic signalling [2], another second study found a minority reacted with live neurons and with no decrease in synaptic or extrasynaptic NMDAR observed [31]. However, clinically, IgA antibodies have been implicated in a slowly progressive cognitive impairment, reversible with immunotherapy [32] and IgA NMDAR seropositivity has also been associated with cognitive dysfunction in a number of cancers, with impairments proportionate to antibody titre and degree of blood brain barrier disruption [3, 33]. Similarly, in a case-control study of people at clinical high risk of psychosis, IgA NMDAR seropositivity was associated with significantly lower IQ and impaired performance on Rey Auditory Verbal Learning Task [4]. These impairments mirror the findings from our study and so it seems possible any antibody-associated effect is not disorder specific with cognitive impairment across a range of clinical populations. However, is also possible that the antibody associated cognitive impairment represents a non-specific factor, indicating patients who have a greater degree of inflammation which could drive clinical outcomes.

Neurofilament light and p-tau181

Plasma NfL is a biomarker of neuroaxonal injury which is not disease-specific [18] while plasma p-tau is an accurate marker of phosphorylated tau [19]. We found NfL concentrations did not differ significantly between PD and HC, consistent with previous studies showing no increase in NfL in PD [34]. Furthermore, we found no association between NfL or p-tau181 levels and NMDAR ab in PD suggesting these antibodies occur independent of the co-existing neurodegeneration and neuro-axonal injury in PD with the frequency of NMDAR ab not related to the degree of neurodegeneration in PD.

NMDAR ab are known to target the NR1 subunit of the receptor causing internalisation and reduction of NMDAR-mediated currents without causing cell death [35]. However, in acute IgG mediated NMDAR encephalitis, there is a significant increase in CSF NfL, which suggests pathological processes extending beyond the reversible internalisation of NMDAR [20]. If IgA or IgM NMDAR ab are exerting an effect in PD, this may be more likely restricted to the synapse, distinct from the inflammatory processes known to occur in IgG NMDAR encephalitis and so without axonal injury and subsequent rise in NfL [36]. Indeed, chronic presence of serum NMDAR ab causes cognitive dysfunction with impairments in spatial working memory and novelty detection in otherwise healthy mice [37]. Indeed, most passive immunisation animal models of NMDAR encephalitis show impairments restricted to cognition, without the diverse symptomology and central nervous system inflammation associated with NMDAR encephalitis in humans [38]. This is not unlike the modest cognitive impairments observed in the current study, and it seems likely that if NMDAR antibodies do have a causative role in neurodegenerative disorders, this is restricted to the synapse, without the additional inflammatory processes inherent to IgG mediated NMDAR encephalitis [36, 38, 39].

Clinical relevance in PD

While overall the aetiology in PD remains to be elucidated there are increasing indicators that neuroinflammation plays a role early in the disease process [40]. Up to 80% of people with PD develop dementia but there is significant heterogeneity in the clinical course and time to develop symptoms. This likely reflects the interplay of many divergent biological factors, of which neuronal autoantibodies could be one. A number of prognostic biomarkers have recently been identified for the cognitive decline in PD, with MRI measures of cortical atrophy and the CSF and blood biomarkers of AD pathology holding particular promise [41]. Indeed, plasma p-tau181 is an accurate marker of phosphorylated tau associated with cognitive decline in neurodegenerative dementia [42, 43]. By showing NMDAR ab to be associated with cognitive decline, independent of p-tau181, we hope to address concerns that the cognitive decline seen in seropositive PD patients exclusively relates to other neurodegenerative processes in PD. Future studies could include a wider array of biomarkers to assess other pathologies implicated in cognitive impairment.

Limitations

In this cohort study, some of the group sizes are small, primarily due to the 44% loss in follow up and the minority of samples with detectable NMDAR ab. Furthermore, although efforts were made to match the PD patients and HC according to age and gender, the availability of HC samples led to a significantly younger patient cohort overall than for the PD patients. No association was found between NMDAR antibody positivity and age and so we do not believe this affects the overall validity of the results. Age was also adjusted for in all regression models.

Not all patients were followed up for the same duration of time after inclusion in the study and, in order to minimise missingness, annual decline in MMSE was calculated from the MMSE scores available over the follow up period. There were not significant differences in the duration of follow up between seropositive and seronegative groups, making this an unlikely confounder and duration of follow up was also included as a covariate in the regression model. The calculated annual MMSE decline demonstrates a difference in MMSE decline of almost 1 point between ab+ and ab- annually, but due to the small numbers in this analysis, the difference did not reach significance outside the regression model.

This study used the MMSE to assess cognition which is known to be less sensitive than the Montreal Cognitive Assessment (MoCA) in PD. However, the MMSE and MoCA are equally sensitive in measuring cognitive change over time in PD and therefore this should not affect the validity of our results [44]. Psychosis, depression and anxiety were assessed in this study with the NMSS and HADS. While these scales offer broad overview of these symptoms, they do not cover neuropsychiatric symptoms comprehensively and are less detailed than other scales. Future studies could consider including NPI or MDS-NMS.

CSF data was not routinely collected in this prospective longitudinal cohort study and so our analysis is restricted to plasma. However, while CSF analysis remains the gold standard for detection in autoimmune encephalitis this does not negate the potential clinical relevance of NMDAR ab found in plasma. Furthermore, previous studies have shown neuronal antibodies are not commonly found in the CSF of dementia populations. [10]

Conclusions

In this longitudinal cohort study we found NMDAR ab seropositivity to be associated with

greater annual cognitive decline in PD. Further investigation is needed to explore whether NMDAR ab have a causative role in the cognitive decline in PD but the reversibility of any immune-mediated mechanism offers exciting potential for therapeutic interventions in the future.

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Conflicts of interest

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

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Table 1. Demographic and biomarker data for HC and PD participants. NfL: neurofilament light.

	HC (n=89)		**PD (n=108)**		**Test statistic**	**p**
	Mean or n	SD or %	Mean or n	SD or %		
Age (years)	54.2	17.0	63.7	11.9	t(195) = -4.59	<0.001
Female (n)	30	34%	27	25%	X^2=1.80	0.18
NMDAR ab+ (n)	3	3.3%	10	9.3%	X^2=2.74	0.10
IgA NMDAR ab+ (n)	0	0%	5	5%	X^2=4.23	**0.04**
NfL concentration[§]	23.5	20.2	25.9	16.3	logNfL	0.08

(pg/ml)					t(141) = -1.73
p-tau18 (pg/ml)	-	-	2.32	1.36	

§ HC n=38

Figure 1. 1A Representative example of NMDAR IgA-positive fixed CBA. 1B Non-transfected IgA control for the same sample. 1C Distribution of NMDAR ab titre by isotype for Parkinson Disease (PD) and Healthy Control (HC) groups.

Table 2. Demographic, clinical and biomarker data based on antibody status.

	IgA/IgM NMDAR ab+ (n=10)		**NMDAR ab- (n=98)**		**Test statistic**	**p**
	Mean or n	SD or %	Mean or n	SD or %		
Age (years)	63.1	9.9	64.6	11.7	t(106)=0.39	0.69
Female (n)	3	30%	24	24%	X^2=0.15	0.70
Education (years)	15.7	4.4	15.9	4.7	*U*=0.27	0.80
Duration with PD (years)	7.3	5.9	6.7	6.2	*U*=-0.33	0.74
Age PD onset (years)	55.8	9.1	57.9	12.5	t(106)=0.51	0.61
Baseline MMSE	28.6	2.1	28.8	2.4	*U*=0.29	0.77
Baseline H&Y scale	2.33	0.5	2.34	0.8	*U*=0.12	0.93
Baseline SCOPA motor score	16.4	9.7	16.8	7.9	t(81)=0.13	0.89
Psychosis at baseline (n)	0	0%	22	22.9%	X^2=2.89	0.09
Baseline HADS	9	6.8	10.5	7.5	*U*=0.55	0.59
Plasma NfL concentration (pg/ml)	31.6	32.4	26.0	14.3	logNfL t(110)=-0.19	0.85
Plasma p-tau181 concentration pg/ml (SD)	1.85	0.25	2.34	1.37	logptau t(109)=1.25	0.21

PD: Parkinson's disease, MMSE: Mini mental state examination, H&Y: Hoehn and Yahr scale, HADS: Hospital Anxiety Depression Scale, NfL: neurofilament light.

Table 3. Longitudinal data stratified by antibody status

	IgA/IgM ab+ (n=7)		**NMDAR ab– (n=54)**		Test statistic	p
	Mean or n	SD or %	Mean or n	SD or %		
Annual decline in MMSE during follow up	1.36	2.55	0.50	0.96	*U*=-0.91	0.36
Cognitive impairment (MMSE<26) in study duration (n)	4	57%	9	17%	X^2=6.05	**0.014**
Emergent psychosis in follow up (n)	3	42.9%	12	22.2%	X^2=1.42	0.23
Change in HADS during follow up	9.4	8.6	6.2	6.0	*U*=-0.93	0.35
Duration of follow up (years)	4.17	1.95	3.6	1.7	t(59)=-0.78	0.44

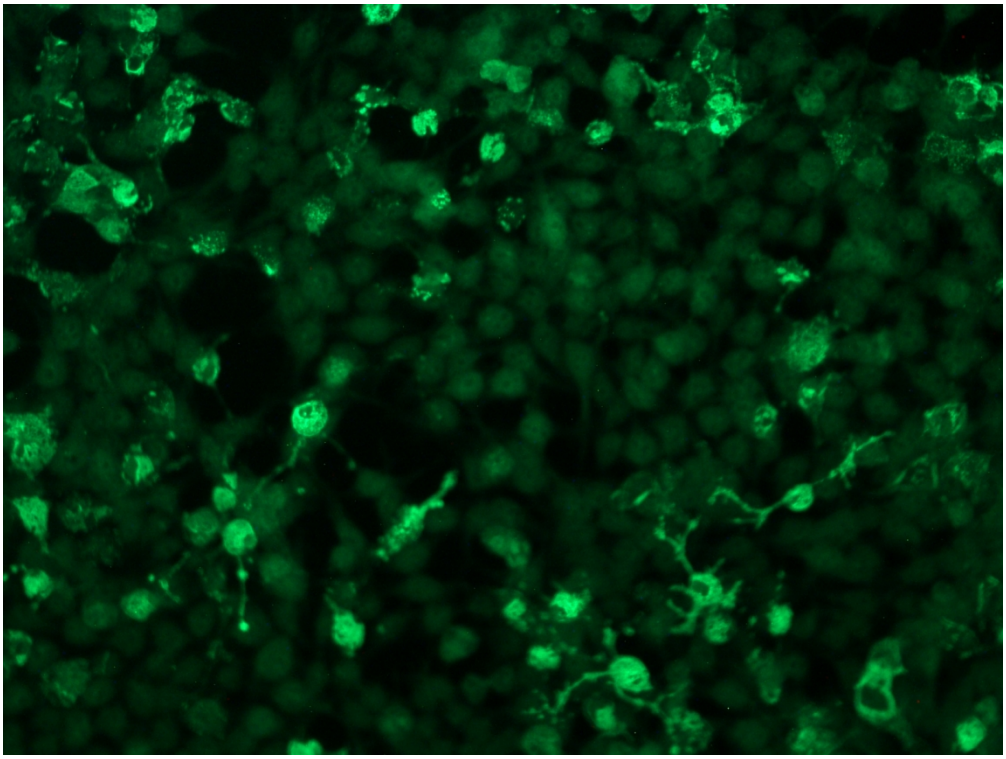
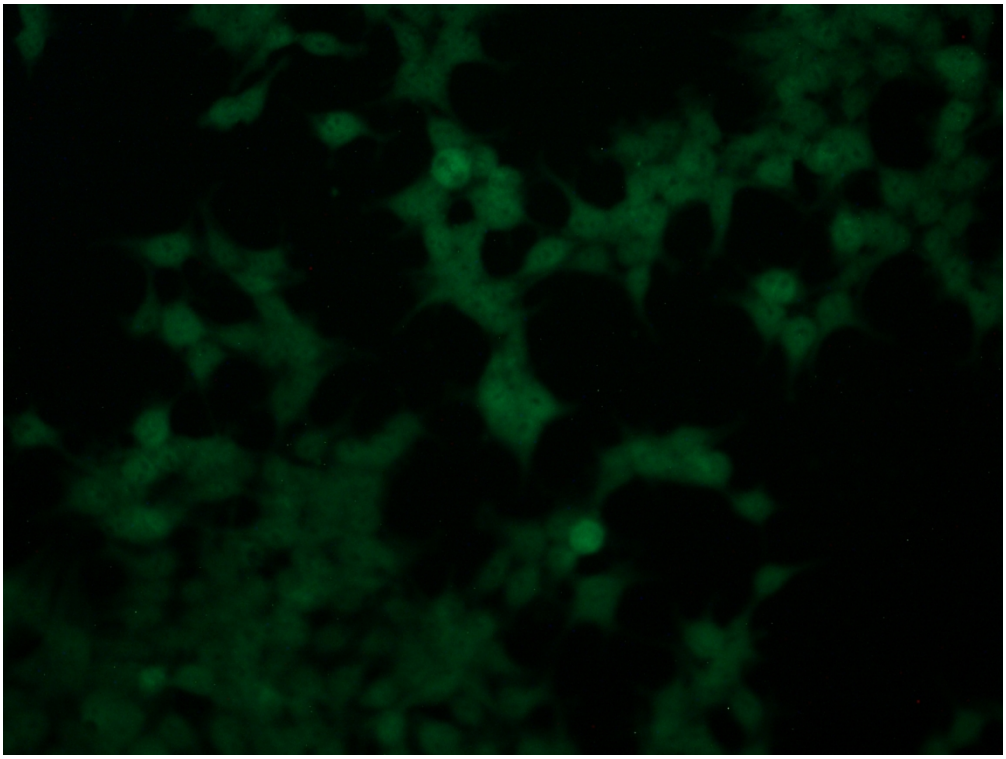


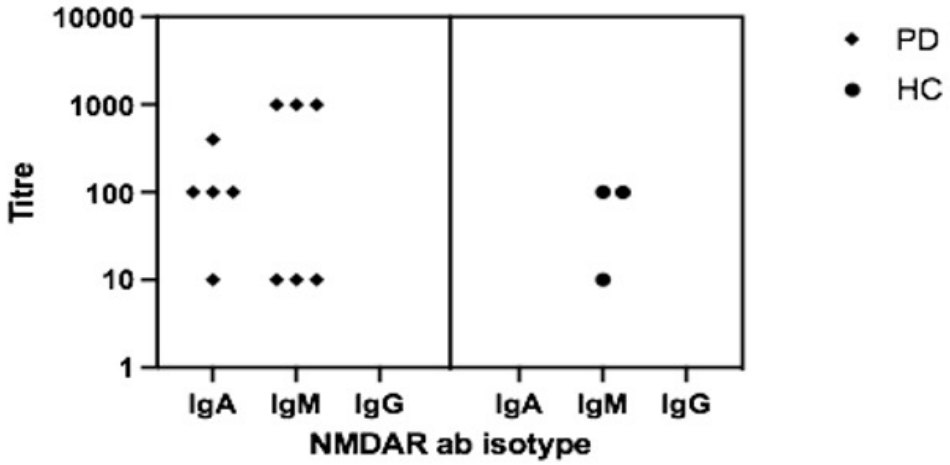
Figure 1. 1A Representative example of NMDAR IgA-positive fixed CBA.

270x203mm (150 x 150 DPI)



1B Non-transfected IgA control for the same sample.

270x203mm (150 x 150 DPI)



1C Distribution of NMDAR ab titre by isotype for Parkinson Disease (PD) and Healthy Control (HC) groups.

112x60mm (144 x 144 DPI)