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Metabolic patterns associated with survival in PSP/CBS: An ^{18}FDG PET voxel-based analysis

Florian Amtage[a,b,*], Michel Rijntjes[a,b], Lars Frings[c,d], Cornelius Weiller[a,b], Philipp T. Meyer[c], Sabine Hellwig[c]

[a] Department of Neurology, University Medical Center Freiburg, Breisacher Str. 64, 79106 Freiburg, Germany
[b] Freiburg Brain Imaging (FBI), University Medical Center Freiburg, Breisacher Str. 64, 79106 Freiburg, Germany
[c] Department of Nuclear Medicine, University Medical Center Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany
[d] Centre of Geriatrics and Gerontology, University Medical Center Freiburg, Lehener Str. 88, 79106 Freiburg, Germany

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ABSTRACT

The four-repeat (4R) tauopathies progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) as atypical parkinsonian syndromes are characterized by rapid disease progression and short survival times. We investigated metabolic patterns depicted by positron emission tomography with [^{18}F] fluorodeoxyglucose (^{18}FDG PET) that may predict overall survival in 4R tauopathies. Thirty-one patients with a clinically diagnosed PSP ($n=23$) or corticobasal syndrome (CBS; $n=8$) underwent an extended follow-up up to 5.4 years after prospective ^{18}FDG PET imaging. On the basis of follow-up data, patients were allocated to the following subgroups: deceased patients with survival time after imaging up to 2.5 years; 2.51–3.5 years; > 3.5 years; and patients still alive at follow up ($\geq$3.49 years). Associations between survival and regional cerebral glucose metabolism were analyzed by statistical parametric mapping (SPM), including patient age at PET as covariate. Twenty patients deceased during follow-up ($n=7$, 8 and 5 at $\leq$2.5, 2.51–3.5 and >3.5 years after PET imaging, respectively); 11 patients were still alive at follow-up (3.49–4.89 years). Analysis of covariance revealed that reduced regional glucose metabolism in left sided sensorimotor area and adjacent parietal and frontal regions areas were significantly associated with shorter survival times. A regression analysis including data of all patients deceased showed additional clusters of hypometablism in left anterior cingulate gyrus and midbrain. 4R tauopathies show distinct metabolic patterns associated with survival, which resemble *post mortem* stages of disease-specific spreading of tau pathology.

1. Introduction

Atypical parkinsonian syndromes (APS; including multiple system atrophy [MSA], progressive supranuclear palsy [PSP], and corticobasal degeneration [CBD]) are characterized by rapid progression to disability and death. APS show shorter survival times when compared to Parkinson's disease (PD) [1–11]. Thus, reliable prognostic stratification is desirable in patients with suspected APS for optimal treatment and counseling.

Among APS, PSP and CBD are histopathologically classified as 4-repeat (4R) tauopathies [12]. According to clinical and clinico-pathological studies, PSP and CBD share comparably short survival times of about 7–8 years from symptom onset or less than 3–4 years from clinical diagnosis [1–5,10,13]. Of note, a marked variation in disease duration has been reported: in CBD/CBS patients survival time ranged between 2.5 and 12.5 years [8], whereas in PSP patients survival times of 2.2 up to 18 years were found [1].

Based on a quantitative tau pathology assessment one *post mortem* study demonstrated that in PSP patients survival time is negatively correlated with tau burden [14]. Furthermore, this study described a general topographical pattern of distribution of tau pathology in PSP, which appeared remarkably consistent despite the diversity of clinical features [14]. Williams et al. identified pons, cerebellum, midbrain and fronto-parietal cortices as strategic regions of tau pathology associated with greater disease severity [14].

Disease-specific patterns of regional cerebral glucose metabolism (as a marker of neuronal activity and, consequently, neuronal dysfunction and degeneration) depicted by positron emission tomography with [^{18}F]fluorodeoxyglucose (^{18}FDG PET) allow for a

* Corresponding author at: Department of Neurology, University Hospital Freiburg, Breisacher Str. 64, 79106 Freiburg (Germany). Fax: +49 761 270 53900.
E-mail address: amtage@neuropsych-waldkirch.de (F. Amtage).

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highly accurate differential diagnosis between PD and APS [15–17] and generally agree with the pattern of pathological involvement in these diseases [14,17,18]. Moreover, a recent study found that ^{18}FDG PET is an early predictor of overall survival in patients with clinically-suspected APS [13].

Against this background, we investigated whether distinct metabolic patterns depicted by ^{18}FDG PET are associated with survival and survival time (as a surrogate of disease progression) in PSP and CBS. We performed an extended survival follow-up of a patient cohort of an earlier prospective study on the diagnostic accuracy of ^{18}FDG PET [13,15]. We compared regional cerebral glucose metabolism across different subgroups using a voxel-based approach as a prognostic marker for survival.

2. Patients and methods

2.1. Study approval and patients

All procedures were approved by the local ethics committee. Written informed consent was obtained from all participants. The initial study was registered at the German Clinical Trials Register (DRKS00003613).

The present study population has been reported before [15,19]. Ninety-five of 107 (88.8%) patients referred for diagnostic imaging between July 2008 and January 2011 for clinically suspected, but not yet verified early-stage APS (based on clinical symptoms and poor response to levodopa; Karnofsky score $\geq$40% and no relevant impairment or reduction or life expectancy caused by other diseases) gave written informed consent.

After a median follow-up of 12 months (minimum 6 months) two board-certified neurologists specialized in movement disorders and blinded for aforementioned imaging results made the clinical diagnosis in accordance to consensus criteria [20]. Seventeen patients were excluded because the clinical follow-up indicated a diagnosis other than a neurodegenerative parkinsonian syndrome. All patients underwent an extended follow-up to 5.4 years after prospective ^{18}FDG PET imaging [13]. Patients were categorized as CBS when apraxia, cortical sensory loss and/or alien limb phenomena were present in combination with an asymmetric hypokinetic disorder often associated with limb dystonia. Patients were categorized as PSP using the following criteria: PSP-RS (Richardson-syndrome; i.e. axial hypokinetic-rigid syndrome in combination with falls within the first 2 years after onset (the onset criteria was adapted on [21]) and supranuclear vertical gaze palsy [22]), PSP-P (PSP-parkinsonism; i.e. asymmetric disease, bradykinesia, limb dystonia, tremor, early dysphagia and initial levodopa response [21]) and as PSP–PAGF (PSP-pure kinesia with gait freezing, but no rigidity or tremor [23]). Thirty-one out of these 95 patients (32.6%) were diagnosed as either CBS (n = 8) or PSP (n = 23) and included in the present analysis. Table 1 summarizes Patients' characteristics.

2.2. ^{18}FDG PET

PET scans were acquired as described previously [15]. In brief, PET scans were acquired on the same ECAT EXACT 922/47 scanner (Siemens-CTI, USA). Starting 40 min after injection of ^{18}FDG (298 $\pm$ 28 MBq), four 5-min emission frames were collected in 2-dimensional mode. Emission frames were reconstructed by filtered back-projection (Shepp filter, 5 mm full width half maximum, FWHM) with subsequent calculated attenuation correction. The summed dataset was used for further analyses.

Table 1
Patients' characteristics.

Clinical diagnosis	Gender	Age at ^{18}FDG-PET [years]	Vital status	Disease duration [years]	Time from ^{18}FDG-PET to follow up or death [years]	Falls within the 1st/2nd year	Upward/downward gaze palsy	Cortical sensory loss/alien limb phenomenon	UPDRS III/modified Hoehn & Yahr scale at ^{18}FDG-PET
PSP	Female	75.8	Alive	9.7	3.49	−/+	+/−	−/−	46/5.0
PSP	Male	64.3	Alive	4.4	3.68	+/+	+/+	−/−	36/4.0
PSP	Female	75.6	Alive	7.5	3.68	+/+	+/+	−/−	50/4.0
PSP	Male	67.2	Alive	8.7	4.04	+/+	+/−	−/−	45/3.0
PSP	Female	65.1	Alive	6.7	4.07	−/+	−/−	−/−	19/2.5
PSP	Female	76.2	Alive	5.5	4.29	+/+	+/+	−/−	34/4.0
PSP	Female	42.6	Alive	7.6	4.55	−/−	+/−	−/−	11/1.0
PSP	Male	59.8	Alive	6.7	4.88	+/+	+/−	−/−	32/4.0
PSP	Male	60.7	Alive	6.8	4.89	+/+	+/+	−/−	28/4.0
PSP	Male	60.0	Dead	4.0	1.52	+/+	+/+	−/−	8/2.5
PSP	Male	70.9	Dead	4.4	1.69	−/+	+/+	−/−	17/3.0
PSP	Male	79.9	Dead	3.7	2.36	−/+	−/−	−/−	33/2.5
PSP	Female	81.5	Dead	8.9	2.45	−/−	+/−	−/−	43/3.0
PSP	Female	76.7	Dead	3.9	2.50	−/+	+/+	−/−	53/5.0
PSP	Male	81.5	Dead	4.5	2.84	+/+	+/−	−/−	63/4.0
PSP	Male	71.9	Dead	4.7	2.90	+/+	−/−	−/−	25/3.0
PSP	Female	74.3	Dead	6.6	3.26	+/+	−/−	−/−	32/4.0
PSP	Male	70.1	Dead	5.3	3.34	+/+	−/+	−/−	27/4.0
PSP	Male	79.7	Dead	5.7	3.49	−/+	+/+	−/−	38/2.5
PSP	Female	65.0	Dead	8.1	4.16	−/+	+/+	−/−	5/2.0
PSP	Male	75.1	Dead	5.2	4.49	+/+	+/−	−/−	24/4.0
PSP	Female	60.0	Dead	8.7	4.65	+/+	+/+	−/−	11/4.0
PSP	Male	62.7	Dead	1.4	4.68	−/−	−/−	−/−	30/3.0
CBS	Female	66.7	Alive	9.7	4.42	−/−	+/+	−/+	27/4.0
CBS	Female	60.8	Alive	9.7	4.77	−/−	−/−	+/+	23/1.0
CBS	Female	74.0	Dead	6.7	0.51	+/+	+/−	−/+	62/5.0
CBS	Memale	72.0	Dead	3.0	1.52	−/−	+/−	−/+	37/4.0
CBS	Female	65.8	Dead	6.2	2.53	−/−	+/−	−/+	46/5.0
CBS	Male	80.6	Dead	8.0	3.06	+/+	−/−	+/+	36/4.0
CBS	Female	64.2	Dead	6.8	3.14	−/−	−/−	+/+	36/3.0
CBS	Male	56.8	Dead	7.2	4.13	−/−	−/−	−/+	47/4.0

PSP = progressive supranuclear palsy; CBS = corticobasal syndrome.