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FDG- and Dopa-PET in postencephalitic parkinsonism

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Summary. We report a case of a 74-year old woman who following an acute virus encephalitis developed an akinetic-rigid Parkinson syndrome with tremor, hypokinesia, hypomimia, rigidity and cogwheel phenomenon in all four extremities, brady-dysdiadochokinesia as well as myoclonic jerks of the arms. Many of the clinical features of this postencephalitic parkinsonism (PEP) suggested the diagnosis of sporadic encephalitis lethargica, first described by von Economo 1917. Cerebral spinal fluid showed signs of a viral encephalitis, and a positive influenza A IgA-antibody titer (1:>160) in the viral serologic screen was found. Positron emission tomography (PET) showed an altered pattern of glucose- and dopa-metabolism clearly different from findings in idiopathic Parkinson syndrome (IPS). The acute lack of inhibitory input from the substantia nigra pars compacta to the striatum could explain the different metabolic patterns in our case in comparison to IPS patients. Our findings indicate that PEP may also be caused by influenza A and furthermore that PET clearly distinguishes PEP from IPS.

Keywords: Viral encephalitis, encephalitis lethargica, postencephalitic parkinsonism, influenza A, positron emission tomography.

Introduction

Postencephalitic parkinsonism (PEP) has been frequently observed with encephalitis lethargica, first described by von Economo (1917). However, after a pandemic in the early 20th century, the disease has virtually disappeared, and its viral etiology has never been established (Casals, 1998). Today, PEP is rarely observed. In the sporadic cases where a viral encephalitis leads to the development of an extrapyramidal syndrome, the question arises whether this syndrome of PEP represents a direct sequela of the encephalitis, or if it is caused by the unmasking of a pre-existing, so far asymptomatic idiopathic Parkinson syndrome (IPS) on the occasion of an acute inflammatory disease of the brain. Positron emission tomography (PET) using tracers of regional cerebral glucose metabolism and dopamine decarboxylation may be helpful to establish this differential diagnosis.

Case report

M.M. is a 74-year-old woman without any medical problem in her history except for a mild arterial hypertonia and a strumectomy 25 years ago. Two weeks before admission, she developed an influenza infection with progressive muscle weakness, and subsequently a bilateral extrapyramidal syndrome with resting and holding tremor, hypokinesia, hypomimia and microphonia. Upon admission, physical examination showed rigidity and a positive cogwheel phenomenon in all four extremities, brady-dysdiadochokinesia and myoclonic jerks of the arms which increased in frequency during intended movements. During the next days she showed an increase of the tremor accompanied by a reduction of vigilance. At this time the body core temperature was 38.5°C, blood pressure and pulse rate were normal. Physical and X-ray examination of the chest disclosed no pathological findings. There were no signs of meningeal irritation. The serologic screening was without pathological results except for a positive influenza A IgA-antibody titer (1:>160) upon admission. This serum titer was indicative of an acute influenza A-infection and declined after one month to normal values.

Upon admission, the cerebrospinal fluid (CSF) contained 390 cells/μl (75% lymphocytes and 25% monocytes) with a protein content of 1,1 g/L. Additionally, there was intrathecal IgG-, IgA- and IgM-synthesis with a disruption of the blood-brain-barrier, oligoclonal IgG bands and an intrathecal antibody-synthesis against measles- and rubella-antigen. No micro-organisms were found on Gram or Ziehl-Neelsen stain. The polymerase chain reactions (PCR) for detection of herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegaly virus (CMV) and enteroviruses from CSF were negative. There was no intrathecal IgG-synthesis against HSV, VZV and Borrelia burgdorferi.

Repeat EEG recordings showed diffuse, moderate slowing with a frontal maximum of theta-delta waves. There were no changes in EEG during electromyographically documented myocloni of the arms. Tremor analysis showed an irregular synchrone 7–9 Hertz action tremor with accentuation under provocation with counting. Cerebral computed tomography was normal. Magnetic resonance imaging (MRI) scans showed only discrete bilateral parieto-occipital leucodystrophic alterations and a beginning brain involution concordant to the patients age (Fig. 1). In the neuropsychological examinations, M.M. reached 25 of 30 possible points in the Mini-Mental-Status-Examination (MMSE) and showed a memory function below average, thought retardation and word finding difficulties.

Two weeks after admission (four weeks after symptom onset), positron emission tomography (PET) scans were performed on subsequent days on a high resolution PET scanner (ECAT EXACT HR, Siemens CTI, Knoxville, USA) (Wienhard, 1994) with [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]fluorodopa (FDOPA) and were coregistered to the patients' MRI scans. Details of the PET scanning procedures have been published elsewhere (Heiss, 1984; Holthoff-Detto, 1997). Due to the limited cooperation of the patient an absolute quantification of the FDG scan was not possible. The metabolic pattern of cerebral glucose consumption showed a marked discrepancy between the values of the putamen and caudate nucleus in relation to cortical regions (Fig. 1). To compare regional values of striatal glucose metabolism, regional metabolic measurements were normalized by cortical values ($rCMR_{glc}$ / $coMR_{Glc}$) (Antonini, 1995). We found a marked difference between the striatal ratios of the PEP patient and the values in normal controls or corresponding Parkinson patients with different Hoehn and Yahr stages (Table 1).

Analysis of the FDOPA-PET data using the graphical analysis approach by Patlak and Blasberg (1985) showed a discrete reduction of the influx constant K_i in both caudate nuclei and a marked reduction in the putamen which, however, lacked the anterior-posterior gradient which is typical for the idiopathic Parkinson syndrome (IPS) (Holthoff, 1994; Morrish, 1996) (Table 1).

With the presumptive diagnosis of viral encephalitis and postencephalitic parkinsonism (PEP), the patient received aciclovir 750 mg t.i.d. intravenously for 14 days follow-

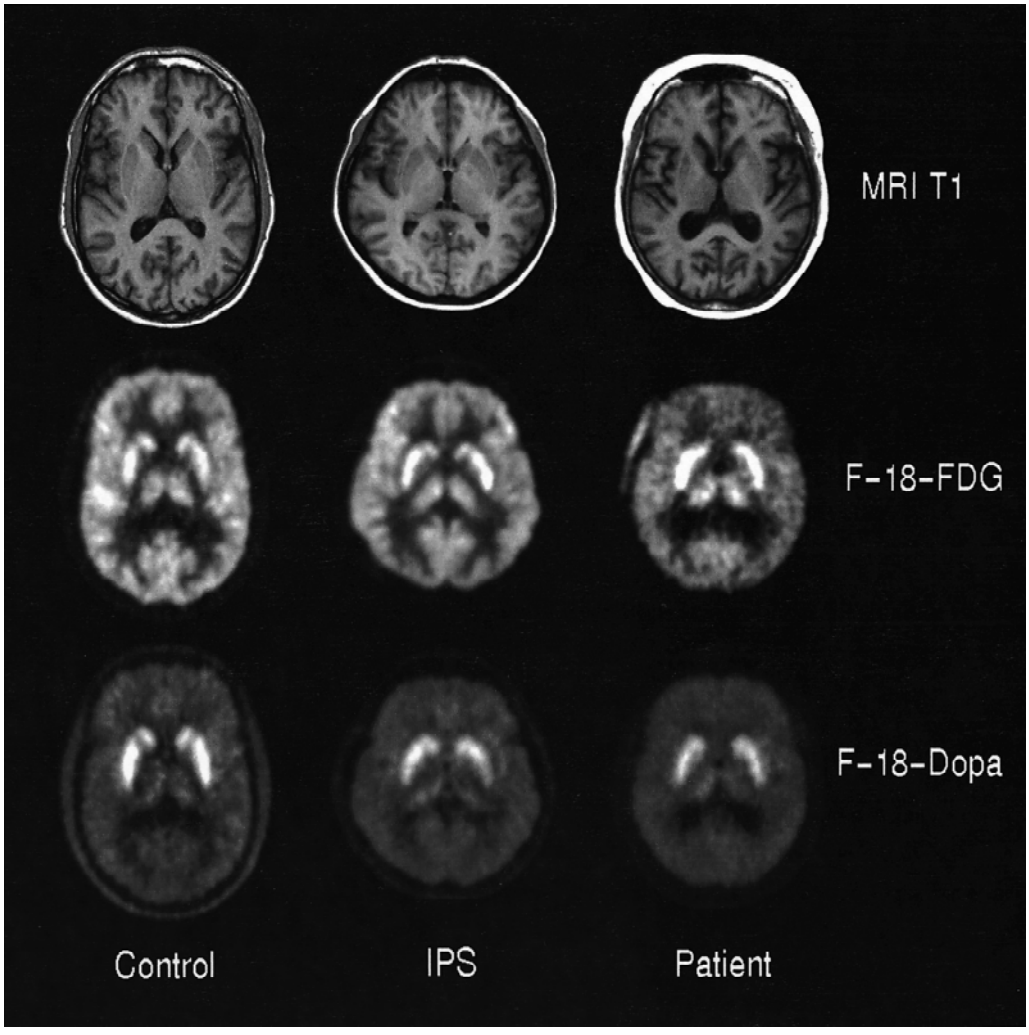

Fig. 1. T1 weighted magnetic resonance imaging (MRI T1), positron emission tomography with [^{18}F]fluorodeoxyglucose (F-18-FDG) and [^{18}F]fluorodopa (F-18-DOPA) in a control (left row), a patient with an idiopathic parkinson disease (IPS) Hoehn & Yahr stage I (middle row) and the patient with postencephalitic parkinsonism (right row). See the marked discrepancy between the striatal glucose metabolism of the patient with PEP in comparison to the cerebral glucose rates of a normal control and an IPS patient (middle row). Additionally, F-18-Dopa-PET shows an anterior-posterior gradient in IPS, which is absent in the PEP patient (lower row)

ing admission. Further treatment included amantadine 200 mg i.v. per day both to alleviate parkinsonian symptoms and as antiviral agent aiming at the influenza A infection. Under this therapy the CSF pleocytosis decreased to 31 cells/μl after 4 weeks. Additionally, the patient received valproic acid for therapy of the myoclonic jerks. The clinical condition of the patient considerably improved and she was transferred to a rehabilitation center 5 weeks after admission. In the 2 months follow-up clinical examination M.M. showed further improvement of her neurological disabilities.

Table 1. Regional striatal glucose ratios [regional striatal metabolic measurements were normalized by cortical values ($rCMR_{Glc}$ / $coMR_{Glc}$)] and Dopa K_i values (min^{-1}) in the caudate nucleus, anterior and posterior putamen in 7 normal subjects, in two groups of parkinson patients (group 1: hemiparkinson patients n = 10; group 2: advanced parkinson patients n = 7) and in the case with a postencephalitic parkinsonism (PEP). Putaminal Dopa-values in the PEP patient shows a marked reduction but without the anterior-posterior gradient which is typical for IPS patients. In contrast to normal controls and IPS patients, the striatal glucose ratios of the PEP patient shows high ratios especially in the right putamen

Tracer	region	normals n = 7	hemiparkinson patients n = 10		advanced PD patients n = 7	PEP	
			ipsilateral	contralateral		left	right
F-18-Dopa	caudate nucleus	0,0095 ± 0,0008	0,0110 ± 0,0024	0,0107 ± 0,0025	0,0070 ± 0,0017**	0,0068	0,0075
	anterior putamen	0,0113 ± 0,0014	0,0113 ± 0,0032	0,0097 ± 0,0026	0,0046 ± 0,0014**	0,0058	0,0051
	posterior putamen	0,0114 ± 0,00090	0,0082 ± 0,0017**	0,0053 ± 0,0013**	0,0023 ± 0,0009**	0,0052	0,0050
F-18-FDG	caudate nucleus	1,08 ± 0,05	1,03 ± 0,07	1,00 ± 0,05	0,98 ± 0,07	1,35	1,33
	putamen	1,20 ± 0,14	1,15 ± 0,09	1,15 ± 0,09	1,17 ± 0,13	1,45	1,66

** $p < 0.005$

Discussion

The patient described in this study presented with an extrapyramidal syndrome with akinetic-rigid parkinsonism that started during and persisted after a viral encephalitis which was diagnosed by CSF examination (390 cells/µl, intrathecal IgG-, IgA- and IgM-synthesis with a disruption of the blood-brain-barrier, oligoclonal IgG bands and an intrathecal antibody-synthesis against measles- and rubella-antigen). Many of the clinical features of our patient (namely reduction of vigilance, parkinsonian symptoms and myoclonus) suggested the diagnosis of sporadic encephalitis lethargica, first described by von Economo (1917). The etiology of von Economo's disease, including the postencephalitic parkinsonism, is still unknown. Von Economo assumed an etiological association between influenza and encephalitis lethargica due to the fact that he observed his first cases during the influenza pandemic of 1918–1919 (von Economo, 1931). However, parkinsonian syndromes have been observed secondary to infections with poliovirus, coxsackie B2, echovirus, arbovirus, measles, chickenpox or herpes simplex virus (Casals, 1998). These data contradict the idea of encephalitis lethargica as a nosological entity associated with a specific single virus only. So far, postencephalitic parkinsonism has not been described following influenza A infection, as most cases of influenza with CNS-symptoms appear to be instances of encephalopathy with brain congestion, edema and swelling, which was considered to be a reactive process to a systemic infection and/or its treatment (Casals, 1998). However, the finding of a serum influenza A IgA-antibody titer of $1:>160$ in our patient clearly indicates that influenza A may also be associated with encephalitis and PEP. Other etiologies, e.g. infections with HSV, VZV, CMV, enteroviruses and Borrelia burgdorferi were excluded by PCR or ELISA with calculation of the antigen specific antibody index. The intrathecal antibody production against measles and rubella antigen may be explained as an unspecific bystander reaction (Reiber, 1991).

M.M. fulfilled most of the diagnostic criteria of the akinetic-mute form of the acute encephalitis lethargica characterized by von Economo (1931) and presented with resting and holding-tremor, hypokinesia, hypomimia, microphonia, cogwheel-phenomenon, brady-dysdiadochokinesia, myoclonic jerks of the arms and reduction of vigilance. Furthermore, M.M. fulfilled the additional diagnostic criterias proposed by Rail et al. (1981) and showed pleocytosis, elevated protein content and oligoclonal bands in the CSF as well as EEG alterations. However, it has to be discussed that the patient suffered from preexisting, yet asymptomatic idiopathic parkinson syndrome (IPS) which exacerbated during a viral encephalitis. For differential diagnosis, we performed positron emission tomography (PET) scans to measure cerebral glucose metabolism and cerebral dopa-decarboxylation. Contrary to the typical findings in IPS with normal values of regional cerebral glucose metabolism (Antonini, 1997) and an anterior-posterior putaminal gradient in FDOPA-PET (Holthoff, 1994; Morrish, 1996) we found a different glucose- and dopa-metabolism in our patient: The glucose metabolism of the striatum was distinctly higher than in the cortical structures and showed a different regional

pattern compared to IPS patients and control subjects (Fig. 1). In our patient, the K_i influx constants of the putamen were homogenously reduced and did not show the anterior-posterior gradient which is typically seen in IPS patients (Holthoff, 1994; Morrish, 1996) (Table 1). This difference from the findings in IPS may be due to the fact that in PEP there is diffuse involvement of the substantia nigra pars compacta (Bernheimer, 1973), while in IPS, there is a ventrolateral predominance of the lesion sites. These PET findings could be explained with a local immunologic pathology, as cerebral alterations in PEP are not of toxic, but inflammatory origin. Similar findings of increased striatal metabolism were observed in Sydenham's Chorea, another postinfectious extrapyramidal syndrome (Goldman, 1993).

These findings stand in contrast to the results of Picard et al. (1996) who found an almost normal glucose metabolism in a case of PEP, except for a slight asymmetry of striatal metabolism and K_i influx constant distributions similiar to values of patients with IPS. However, the patient described by Picard et al. had an encephalitic syndrome associated with a prolonged lethargic state at the age of 5 years and was investigated with PET more than thirty years later. Caparros-Lefebvre et al. (1998) reported a case of a 76-year old woman who had been affected by encephalitis lethargica in 1918, at the age of 3 months. The patient demonstrated a severe bilateral and symmetrical reduction in F-18-Dopa, which was more marked in the putamen than in the caudate nucleus. Additionally, they performed HmPaO-SPECT which was normal and without striatal hypoperfusion. But as their patient was studied many decades after the acute disease, it has to be discussed whether the alterations described really reflect sequelae of the encephalitis lethargica, rather than age-related changes of dopa-decarboxylation.

To our knowledge, our PET study is the first investigation in acute PEP. It shows a marked difference between the glucose and dopa-metabolism of a PEP patient and IPS patients. In a post mortem study of PEP, the neuronal population was devastated throughout the zona compacta of the substantia nigra (Bernheimer, 1973). The striatal glucose hypermetabolism in our PEP patient may be due to an acute lack of inhibitory dopamin input from the substantia nigra pars compacta to the striatum which stands in contrast to the slower disease progress in IPS (Conrad, 1996). These PET findings clearly distinguish PEP from IPS. In contrast to IPS, PEP is not a primary neurodegenerative process associated with a progressive decline of dopa-metabolism that leaves cerebral glucose metabolism nearly unaltered.

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