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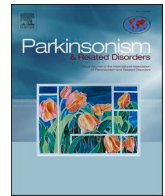
The neurological and neuropsychiatric spectrum of adults with late-treated phenylketonuria

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ABSTRACT

Introduction: Phenylketonuria (PKU) is a rare, treatable inborn error of metabolism with frequent neurological and neuropsychiatric complications, especially in undiagnosed or insufficiently treated individuals. Given the wide range of clinical presentations and the importance of treatment implications, we here delineate the neurological and neuropsychiatric symptom spectrum in a large cohort of previously unreported adults with late-treated PKU.
Methods: We consecutively evaluated late-treated PKU cases and pooled clinical and paraclinical data, including video-material, from three centers with expertise in complex movement disorders, inborn errors of metabolism and pediatrics.
Results: 26 individuals were included (10 females, median age 52 years). Developmental delay and intellectual disability were omnipresent with severe impairment of expressive communication noted in 50% of cases. Movement disorders were prevalent (77%), including tremor (38%, mostly postural), stereotypies (38%), and tics (19%). One case had neurodegenerative levodopa-responsive parkinsonism. Mild ataxia was noted in 54% of cases and 31% had a history of seizures. Neuropsychiatric characteristics included obsessive-compulsive (35%) and self-injurious behaviors (31%), anxiety (27%), depression (19%) and features compatible with those observed in individuals with autism spectrum disorder (19%). Neuroimaging revealed mild white matter changes. Adherence to dietary treatment was inconsistent in the majority of cases, particularly throughout adolescence.
Conclusion: A history of movement disorders, particularly tremor, stereotypies and tics, in the presence of developmental delay, intellectual disability and neuropsychiatric features, such as obsessive-compulsive and self-injurious behaviors in adults should prompt the diagnostic consideration of PKU. Initiation and adherence to (dietary) treatment can ameliorate the severity of these symptoms.

1. Introduction

Inborn errors of metabolism encompass a heterogeneous group of disorders, where metabolic pathway defects affect different systems and organs with frequent central nervous system involvement. For some of these conditions, clinical presentations or paraclinical findings, such as

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neuroimaging, may be pathognomonic. However, in many inborn errors of metabolism the range of clinical manifestations can be broad, and, therefore, knowledge on the entire spectrum of different phenotypes is necessary to guide diagnosis and inform appropriate treatments.

Phenylketonuria (PKU) is a rare, treatable inborn error of metabolism caused by autosomal recessive mutations in the *PAH* gene coding for the phenylalanine hydroxylase (PAH) enzyme. *PAH* catalyzes the conversion of phenylalanine (phe) to tyrosine, a precursor for monoamine neurotransmitters. In PKU, increased phe blood levels, disturbed monoamine neurotransmitter synthesis, and accumulation of other intermediate metabolic products lead to neurodevelopmental delay and severe disability, including movement disorders [1], as Fölling first described in 1934. Early diagnosis and prompt introduction of dietary treatment to reach immediate metabolic control typically prevent the development of severe neurological and neuropsychiatric sequelae [1].

Neonatal screening for PKU has been implemented in many parts of the world throughout the 1970s. Since then, untreated cases have been drastically reduced. However, neonatal PKU screening is not universal. For example, many countries have not introduced PKU screening yet or did so only recently, and nationwide coverage may not always be present [3]. Moreover, false-negative screening results may occur. It is, therefore, important to consider that PKU may still go undiagnosed and treatment initiation may often be delayed, particularly for adults born before the implementation of screening programs.

Previous studies mainly focused on clinical characteristics of early-treated patients [2]. Given the scarcity of systematic data on the spectrum of neurological and neuropsychiatric symptoms in adults with late-diagnosed and -treated PKU, we here provide a detailed account on the clinical characteristics of a large cohort of 26 adult cases, accompanied with illustrative video-documentation. Our goal is to reposition PKU in the differential diagnosis of adult cases, specifically where neurological signs, particularly movement disorders, and neuropsychiatric features co-occur.

2. Methods

Adults with late-treated PKU (i.e., diagnosis was made and/or stable diet was introduced only after 12 weeks after birth) were included in our study. All individuals were neurologically evaluated by pediatricians with expertise in neurology and movement disorder specialists. Clinical data were pooled from three centers (Charité University Medicine Berlin, Berlin, Germany; P.J. Safarik University/University Hospital L. Pasteur, Košice, Slovakia; Klinikum Reutlingen, Reutlingen, Germany). We reviewed medical charts and collected clinical and paraclinical information including sex, age and main neurological and neuropsychiatric features at the time of diagnosis and during last examination, age at dietary introduction, as well as adherence to diet. We also included documented comorbidities and current medication. The serum phe-level at last follow-up, as well as results from genetic analyses and magnetic resonance imaging of the brain, if available, were also collected. Characteristic video-documented examples of the motor and neuropsychiatric symptom spectrum in individuals with late-treated PKU are also provided. Participants and/or their legal guardians gave written informed consent for online video publication and dissemination. If not indicated otherwise, data are presented as median and interquartile range (IQR). The study was approved by the local ethics committee of the Charité University Medicine Berlin (registration number EA1/203/20).

3. Results

We included 26 late-treated cases of PKU (10 females), none of which has been previously reported. Median age at the time of assessment was 52 years (IQR, 35–57 years). Diagnosis was made on basis of largely elevated plasma phe levels and pterin analysis in all cases. In addition, genetic analyses of *PAH* were available for 17 cases. In most cases exonic

mutations, including 6 homozygous R408W mutations, were found. Intronic mutations were additionally documented in 4 cases (no. 7, 9, 10, and 20). Median age at diagnosis was 3 years (IQR, 1–5.5 years). A positive family history (affected siblings) was present in 4 cases and two individuals were brothers (case 5 and 6). Detailed case descriptions can be found in Table 1.

3.1. Neurological findings

Abnormal neurological findings were documented in all adults at the time of presentation. A previous history of developmental delay was omnipresent, and in 13 cases (50%) severe impairment of speech was noted (see video examples 1A-C and F). Seizures had been documented in 8 cases (31%) (n = 1, West syndrome, n = 1, hypsarrhythmia, n = 1, complex focal seizures, n = 5, not otherwise specified).

On examination, the most common neurological finding was the presence of a movement disorder. 20 patients (77%) had at least one hyperkinetic movement disorder, such as tremor (n = 10, 38%; video 1E), mostly postural tremor of the arms, motor stereotypies (n = 10, 38%; see video 1A-D), and tics (n = 5, 19%; see video 1B, C, F and G). Abnormal posturing of the head (n = 1) and arms (n = 1, see video 1A) were also noted. Hypokinetic movement disorders were only observed in one case, who presented with levodopa-responsive parkinsonism (see video 1H). 14 cases (54%) showed mostly mild limb or gait ataxia (see video 1G). Other abnormalities included brisk reflexes (n = 4, 15%).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2021.06.011

3.2. Neuropsychiatric findings

In all cases intellectual disability, reported to range between mild to severe, had been documented. The intelligence quotient (IQ) was additionally noted in 11 cases (median IQ = 54, IQR, 39–69). Other neuropsychiatric findings included obsessive-compulsive behavior in 9 (35%, mostly behaviors related to ordering and arranging, see Table 1), self-injurious behavior in 8 (31%, see video 1D and E), and aggressive behavior in 7 (27%) cases. Anxiety disorders and depression were documented in 7 (27%) and 5 (19%) cases, respectively. Clinical features compatible with autism spectrum disorder (ASD) were noted in 5 cases (19%).

3.3. Imaging findings

Brain neuroimaging (magnetic resonance imaging, MRI) was performed in 6 cases only (23%). Diffuse white matter changes (n = 3, see Fig. 1A) and gliosis in the frontal superior gyrus (n = 1) were documented, and in two cases brain MRI was reported normal. In the one case with parkinsonian features (case no. 26, also see video description 1H), a 123I-FP-CIT SPECT (DaTSCAN) was performed, which showed reduced tracer uptake in the striatum, particularly in the posterior putamen and pronounced in the left hemisphere (see Fig. 1B).

3.4. Treatment course

In all but 3 cases (no. 10, 16 and 21) diet was introduced promptly after diagnosis. In 14 cases (54%) adherence to diet was inconsistent, and in 9 of those long dietary pauses were documented (median pause 18 years, IQR, 11.5–27.5 years). Diet pauses usually began in adolescence (median age at begin of diet pause 14 years, IQR, 5–15 years). Years without dietary treatment did not significantly correlate with the global clinical impression scale as global measure of symptom severity ($r_s = 0.138$, p = 0.521). At the time of last presentation median blood phe concentration in our cohort was 720 μmol/l (IQR, 306–896 μmol/l). In 6 cases, pharmacologic treatment of neuropsychiatric disorders, including aggression (n = 2) and depression (n = 2) was documented.

Table 1
Clinical characteristics of individuals with late-treated PKU.

Case/ sex	Current age/age at diagnosis (y)	Reason for diagnosis	Years w/o dietary treatment, adherence to diet	Serum-phe level at last follow-up (μmol/l)	Genotype	MRI	CGI	Neuropsychiatric assessment and cognition	Other neuropsychiatric abnormalities	Movement disorders and cerebellar signs	Other neurological signs	Other comorbidities	Current medication
1/m	20/2.5	developmental delay, stereotypies, hypotonia	2.5, unstable diet	902	n/a	normal (2001)	5	ID	OCB (need for order), avoids social contacts, limited set of interests (e.g., colored cables)	Stereotypies (upper body rocking), abnormal posture of the upper extremities	Restricted communication (yes/no), echolalia	Sleep disturbances, eczema, phimosis, hepatomegaly, splenomegaly, stenotic blockage of carotid artery	phe-free amino acid mixture
2/m	37/1	seizures	1, n/a	714	R408W/ R408W	n/a	6	Agitation, IQ < 30	OCB (need for symmetry and order)	Stereotypies, simple and complex vocal and motor tics (sniffing, loud exhalation, nose touching, grimacing)	West syndrome (seizures until the age of 25), restricted communication (yes, fine)	vit D def, zinc def, hay fever	phe-free amino acid mixture, antihistamins
3/m	62/49	developmental delay, ID	49, n/a	260	R408W/ R408W	n/a	5	Aggressive behavior, anxiety, ID	OCB (need for order (e.g., LEGO, tin soldiers), hand washing)	Stereotypic hand movements, tics (grunting, "combing hair", hitting head, nose touching, face scratching, lifting hat, echo- and coprolalia)	Restricted communication (short sentences)	Cardiac insufficiency, vit D def, zinc def	phe-free amino acid mixture, calcium, zinc, vit D, vit C
4/f	58/1.5	seizures	16.5, unstable diet	950	R408W/ R261Q	n/a	5	Depression, nervousness, agitation, IQ = 39	SIB (biting arms)	Stereotypies (upper body rocking), orolingual dyskinesias, gait ataxia	Seizures in childhood (nos), restricted communication, muscle hypertonia, areflexia, pallhypesthesia of the lower extremities	Arterial hypertension, osteopenia, obesity, uterine cancer, disturbed day-night-rhythm	phe-free amino acid mixture, ramipril, risperidone, melperone
5/m	22/*	n/a	3, unstable diet	690	R158Q/ L249H	n/a	3	Aggressive behavior, mild ID, IQ = 60	–	High-frequent postural tremor of the upper extremities, dysdiadochokinesia	Brisk reflexes (lower > upper extremities)	–	phe-free amino acid mixture
6/m	24/5	developmental delay, sibling with PKU	5, n/a	745	R158Q/ L249H	n/a	3	IQ = 68	–	Dysdiadochokinesis	Brisk reflexes (lower extremities)	–	phe-free amino acid mixture
7/f	56/1	hypotonia, developmental delay	20, n/a	321	IVS12+1G > A/ IVS12+1G > A	n/a	4	Mood instability, ID	SIB (picking and tearing fingernails, excessive scratching)	High-frequent postural and mild intention tremor of the upper extremities	Seizures in childhood (nos), spastic hemiparesis on the left (stroke)	Stroke of the right hemisphere, arterial hypertension, osteopenia, psoriasis, psoriatic arthritis, cholecystectomy	phe-free amino acid mixture, valproic acid, olmesartan, amlodipine, methotrexate, folic acid
8/m	57/7	developmental delay	22, unstable diet	896	n/a	n/a	6	Aggressive behavior, anxiety (claustrophobia), severe ID	limited set of interests (e.g., fascination of thunder and handcrafts)	Stereotypies (upper body rocking), tics ("oha", sniffing, turn up nose, shoulder shrugging, tapping on	Restricted communication	Vit D def, osteoporosis, zinc def, hypophosphatemia, hypopotassemia, arterial hypertension, thrombocytopenia,	phe-free amino acid mixture, calcium, zinc, phosphate, melperone

Table 1 (*continued*)

Case/sex	Current age/age at diagnosis (y)	Reason for diagnosis	Years w/o dietary treatment, adherence to diet	Serum-phe level at last follow-up (μmol/l)	Genotype	MRI	CGI	Neuropsychiatric assessment and cognition	Other neuropsychiatric abnormalities	Movement disorders and cerebellar signs	Other neurological signs	Other comorbidities	Current medication
										nose/shoulder), mild gait ataxia, akathisia		urothelial carcinoma, hypoacusis	
9/f	57/2	white hair, developmental delay	20, n/a	848	IVS12+1G > A/F299C	n/a	3	Depression, anxiety (agoraphobia, claustrophobia), IQ = 82	–	Stereotypies (foot rocking, finger rubbing), mild gait ataxia	–	Vit D def, osteopenia, diabetes mellitus type 2, arterial hypertension, hypercholesterolemia, obesity, thyroidectomy after autoimmune thyroiditis, hysterectomy (myomas) and adnexectomy, glaucoma	phe-free amino acid mixture, vit D, metformin, ramipril, levothyroxine, minocycline, brinzolamide/timolol eye drops
10/m	47/2	developmental delay	10, n/a	176	IVS10-11G > A/D84Y	n/a	3	Depression, aggressive behavior, severe ID	SIB (biting skin around fingernails)	Simple motor and vocal tics (blinking, stretching arm muscles, shrugging, humming), mild gait and limb ataxia	Saccadic pursuit, impaired internal vertical saccades	Osteopenia, hypercholesterolemia, obesity, mild renal insufficiency	phe-free amino acid mixture, calcium, fluoxetine
11/m	53/5	developmental delay	5, n/a	726	n/a	n/a	3	Rage, ID	avoids social contacts	Abnormal posture of the head, akathisia	Impaired gaze maintenance, dysarthria	Osteoporosis, zinc def, renal insufficiency	phe-free amino acid mixture, calcium, zinc, lisinopril, mirtazapine
12/m	54/*	developmental delay	n/a[#], unstable diet	981	R408W/R408W	occipital and frontotemporal white matter lesions (1991)	3	Mood instability, anxiety (agoraphobia, claustrophobia), IQ = 52	OCB (need for order), SIB (excessive biting of fingernails)	Mild orofacial dyskinesias, mild intention tremor of the upper extremities, mild ataxia	–	Vit D def, osteoporosis, hypopotassaemia, arterial hypertension	phe-free amino acid mixture, potassium, candesartan, amlodipine, moxonidine, metoprolol
13/f	69/18	developmental delay	18, n/a	509	n/a	gliosis in frontal superior gyrus (2016)	4	Mild ID	OCB (need for order, daily routines), SIB (excessive scratching)	High-frequent, irregular, postural tremor of the upper extremities, intermittent head and leg tremor, ataxic gait	Pallhypesthesia of the lower extremities	Vit D def, arterial hypertension, mild hyperthyreosis, urge incontinence	phe-free amino acid mixture, vit D, ramipril, hydrochlorothiazide, trospium chloride
14/m	52/*	n/a	n/a[#], unstable diet	896	n/a	n/a	3	IQ = 77	–	Postural tremor of the upper extremities, dysdiadochokinesia of the upper extremities	Strabismus, hypometric external saccades, brisk reflexes right leg	Arterial hypertension, benign prostate hyperplasia	phe-free amino acid mixture, vit D, ramipril, tamsulosin
15/m	51/3	developmental delay	3, unstable diet	751	n/a	n/a	3	Moderate ID	OCB (cleaning > 8h/d), SIB (excessive scratching)	Stereotypies (upper body rocking), mild intention tremor of the upper extremities	Mild apraxia, saccadic pursuit, delayed internal and external saccades	Vit D def, arterial hypertension	phe-free amino acid mixture, vit D, olmesartan
16/f	58/8	sibling with PKU	48, unstable diet	336	R408W/R408W	n/a	6	Aggressive behavior, severe ID	avoids social contacts	Stereotypies (upper body rocking), trunk, limb and gait ataxia, unable to walk without support	No verbal communication	–	phe reduced protein supplement (glycomacropeptide)
17/f	57/41	siblings with PKU	41, n/a	188	L48S/R408W	n/a	5	Depression, anxiety, ID	OCB, episodes of hallucination (several years ago)	Stereotypies, mild tremor	Restricted communication (simple sentences)	Sleep disturbances, vit D def, vit B12 def, obesity, mild pancreatitis, gastroesophageal reflux, allergies, intolerance to	phe-free amino acid mixture, vit D zinc, paroxetine, quetiapine

Table 1 (*continued*)

Case/sex	Current age/age at diagnosis (y)	Reason for diagnosis	Years w/o dietary treatment, adherence to diet	Serum-phe level at last follow-up (μmol/l)	Genotype	MRI	CGI	Neuropsychiatric assessment and cognition	Other neuropsychiatric abnormalities	Movement disorders and cerebellar signs	Other neurological signs	Other comorbidities	Current medication
												flavors, increased hair loss, recurrent dermatitis	
18/m	56/3	n/a	36, n/a	1368	n/a	n/a	6	Aggressive behavior, restlessness, anxiety, ID	OCB	Mild dyskinesia, mild ataxia	Restricted communication (simple sentences)	Vit B12 def	vit D, quetiapine
19/m	51/0.75	seizures	0.75, n/a	442	R261Q/Y356X	white matter abnormalities	5	Mood instability, IQ = 54	–	–	Epilepsy (hypsarrhythmia), dysarthria	Osteoporosis, hay fever	phe-free amino acid mixture, vit D, calcium
20/m	52/4	sibling with PKU	4, n/a	886	G239V/IVS10-11G > A	n/a	6	ID	–	Coarse tremor, dyskinesia, limb and gait ataxia	Epilepsy (nos), restricted communication (simple phrases)	–	phe-free amino acid mixture, valproic acid
21/m	44/0.75	developmental delay	1, n/a	1063	L48S/R408W	n/a	4	Depression, anxiety, IQ = 50	OCB, alcohol abuse, delinquent behaviors (repeated theft), psychotic symptoms, difficulties with social interaction	Mild tremor	–	Arterial hypertonia, obesity, recurrent episodes of dizziness	phe free amino acid mixture, quetiapine
22/f	44/7	developmental delay	7, n/a	177.3	R408W/R408W	n/a	6	Aggressive behavior, agitation, restlessness, severe ID	SIB	Stereotypies, tics (head shaking)	Epilepsy (nos), restricted communication (single words)	Sleep disturbances, vit D def, kyphosis, short stature, obesity, chronic cough, habitual polydipsia	phe-free amino acid mixture, vit D, risperidone, olanzapine
23/f	29/3.65	developmental delay	3.65, n/a	415	S310F/R158Q	normal (1994)	4	Attention deficit, IQ = 69	–	Dysdiadochokinesia	–	Ferritin def.	phe-free amino acid mixture
24/f	27/1.25	developmental delay	1.25, n/a	10.3	R408W/R408W	n/a	5	Severe ID	ASD, SIB	Gait ataxia	Epilepsy (complex focal seizures), no verbal communication	Vit D def, short stature	phe-free amino acid mixture, valproic acid, oxcarbazepine
25/f	18/0.75	developmental delay	0.75, n/a	203	n/a	n/a	5	IQ = 39	–	–	One seizure in childhood (nos), restricted communication	–	phe-free amino acid mixture
26/m	53/3	developmental delay	25, n/a	733	n/a	white matter hyperintensities (2012), path. DaTSCAN	4	Apathy, mood instability, mild ID	–	Tics in childhood, right-side dominant akinetic-rigid syndrome and rest tremor, levodopa-induced dyskinesias	Restricted communication (simple sentences)	Hyposmia, urinary urgency, constipation, excessive sleepiness, fatigue, excessive sweating, impulse control disorder	phe-free amino acid mixture, levodopa/carbidopa, amantadine, pramipexole

ASD, autism spectrum disorder, CGI, clinical global impression scale (1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill patients), def, deficiency, ID, intellectual disability, IQ, intelligence quotient, OCB, obsessive compulsive behavior, n/a, information not available, nos, not otherwise specified, SIB, self-injurious behavior, vit, vitamin; in all but 3 cases (case 10, 16 and 21), dietary treatment was introduced promptly after diagnosis; *diagnosis several weeks delayed, #no exact records available, stable dietary treatment introduced after the first years of life.

4. Discussion

In our sample of 26 adults with late-treated PKU, neurological and neuropsychiatric signs were documented in all cases. Developmental delay and intellectual disability were omnipresent, which, in about half of cases, was accompanied by severe impairment of language and communication. Other neurological abnormalities included movement disorders, notably tremor, stereotypies and tics, ataxia, and seizures. One case presented with levodopa-responsive parkinsonism. Obsessive-compulsive, self-injurious and aggressive behaviors, as well as signs of ASD, anxiety and depression were also noted. A summary of our main clinical findings, which may serve as useful diagnostic clues, is provided in Table 2.

4.1. The neurology of adults with late-treated PKU

In contrast to adults with early-treated PKU, where findings are typically mild to moderate (e.g., presence of postural or kinetic tremor, brisk reflexes, poor fine motor skills [2,4]), neurological abnormalities are more severe in late-treated cases. Specifically, beyond the well-established presence of developmental delay in all cases we examined, movement disorders were the most common feature. Mild postural and/or kinetic tremor was noted in 38% of cases, within the overall prevalence range reported for late- (or untreated) individuals with PKU according to a recent meta-analysis (40%, 95% CI: 17–65%) [5]. Tremor in our cases did not typically interfere with the individual's activities of daily life, confirming previous descriptions [5,6]. Interestingly, though mild limb or gait ataxia was present in 54% of cases, this finding was not directly related to the presence of tremor (only 5/14 cases with ataxia had concomitant tremor; also see Table 1). One recent evaluation of six adults with early-treated PKU but without strict dietary compliance early in life also showed ataxia in 50% of patients [7]. This is considerably higher than in a previous study that reported ataxia in only 18% of patients [8]. One possible explanation for the discrepancy might be that limb ataxia is not always unambiguously labeled and previous reports have used terms such as 'clumsiness' or 'difficulties in limb co-ordination' [9], to describe, most likely, ataxic behaviors. The recognition of ataxia in adults with intellectual impairment might therefore serve as an important diagnostic clue for PKU.

Motor stereotypies were documented in 38% and about one fifth of patients we examined presented with motor and/or vocal tics. Previous reports of adults with late-treated PKU documented stereotypies [10,11], which persisted beyond childhood and were associated with intellectual disability, as in our cases. Also, tics have already been described in untreated PKU patients in the 1950s [11], but have not received much attention since [2,6,8,9,12–17]. Importantly, their phenomenology has not been previously delineated. In our cohort, tics were typically mild, and simple tic behaviors prevailed (see Table 1). Different from tics in primary tic disorders, a 'waxing and waning' course was not reported by caregivers in our cases. Of note, one recent population-based study suggested that tics may be 5.4 times more prevalent in individuals diagnosed with PKU than in the general population [18].

In one account the prevalence of tic disorders in PKU might appear somewhat counterintuitive, as deficient tyrosine synthesis leads to a depletion of dopamine in the central nervous system, rather than the dopaminergic hyperinnervation suggested to underlie tic behaviors [19]. In the absence of well-established pathophysiological models for tic-behaviors and stereotypies, it is difficult to provide conclusive remarks on how PKU may predispose to their development. However, this observation suggests that aberrant dopaminergic neurotransmission plays an important role in tic pathophysiology [20]. This notwithstanding, both intellectual disability and motor developmental delay, independent from etiology, have also been linked to stereotypic behaviors and tics [21,22]. However, we do note the high occurrence in our population and suggest that the presence of persistent stereotypic behaviors and tics in adults, particularly in the presence of

developmental delay, should prompt the diagnostic consideration of PKU. We also comment that a clear categorical distinction between stereotypies and tics might be notoriously difficult in some cases, especially in the absence of first-person reports on associated phenomena, such as premonitory urges.

Levodopa-responsive parkinsonism was documented in only one case in our cohort. Several previous case reports also highlighted parkinsonian features in late-treated adults with PKU [14–16,23] and more recently an evaluation of 19 individuals with early-treated PKU documented bradykinesia in 3 cases [4]. The presence of parkinsonian features in PKU has been attributed to the biochemical disruption of dopaminergic pathways due to inhibited amino acid uptake across the blood-brain barrier, blockage of tyrosine hydroxylase and phenylalanine hydroxylase deficiency. In our patient, motor and non-motor symptoms were suggestive of idiopathic parkinsonism (see Table 1, case 26). Indeed, DaTSCAN revealed reduced presynaptic dopamine transporter density (see Fig. 3), possibly favored by the bioaminergic depletion [4]. After introduction of a low-phe diet combined with phe-free amino acid supplementation, tremor and bradykinesia significantly improved in our patient, similar to adults in whom parkinsonism was markedly reduced under a low-phe regimen [14,16]. As in our patient, dopaminergic medication has been reported to ameliorate parkinsonian symptoms in children and adults with PKU [14]. We believe that in our case, PKU co-occurred with neurodegenerative parkinsonism.

We documented the presence of abnormal postures (head and upper extremities) in two cases (case 1 and 11). These postures were not related to additional jerky movements, there were no overflow phenomena and no geste antagoniste, whereby in both cases clinical signs compatible with the diagnosis of autism spectrum disorder were also noted. It is, therefore, difficult to disentangle whether these signs reflect a dystonic disorder or mirror the frequently reported postural changes in individuals with autism spectrum conditions, possibly related to aberrant body perception [25,26]. Of note, dystonia as movement disorder in PKU has only been described in few isolated cases [7].

31% of our patients had seizures during their lifetime which is in line with epilepsy being reported in up to a third of late-treated PKU patients [9,13,17]. Semiology and possible pathophysiological background have been delineated previously [27].

Finally, brisk reflexes as signs of spasticity were rare in our cases (15%) compared to 28% of cases with spasticity in the González-group and to the commonly reported hyperreflexia in early-treated patients [4,8,9]. Brisk reflexes might be associated with frequently described brain white matter lesions, however, may be of negligible relevance to the individual's quality of life.

4.2. The neuropsychiatry of adults with late-treated PKU

Before the introduction of a phe-restricted diet for infants with PKU promptly after diagnosis, the disease typically lead to severe cognitive deficits [28]. Despite availability of treatment, the rate of neuropsychiatric comorbidities in patients with PKU – even in individuals with early-treated PKU – is still higher than in the general population [5]. Moreover, adults who discontinued phe-restricted diet have even higher rates of neuropsychiatric abnormalities compared to individuals who maintained their diet with good metabolic control [29].

Each of our patients either scored low on IQ tests or was diagnosed with mild to severe intellectual disability based on daily living skills and the intensity of support needed to achieve optimal personal functioning [30,31]. Indeed, only 25% of individuals with late-treated PKU reach IQ scores in the normal range [9]. In contrast, IQ levels of early-treated PKU cases are comparatively higher, usually within the normal range [2,6,9,32] and appear to be stable and independent from blood phe-levels once adulthood is reached [33]. Other neuropsychological measures like working memory, attention and response inhibition are influenced by ongoing blood phe-levels: patients with poor dietary compliance perform worse [32,34]. Evidence suggests, that these deficits in
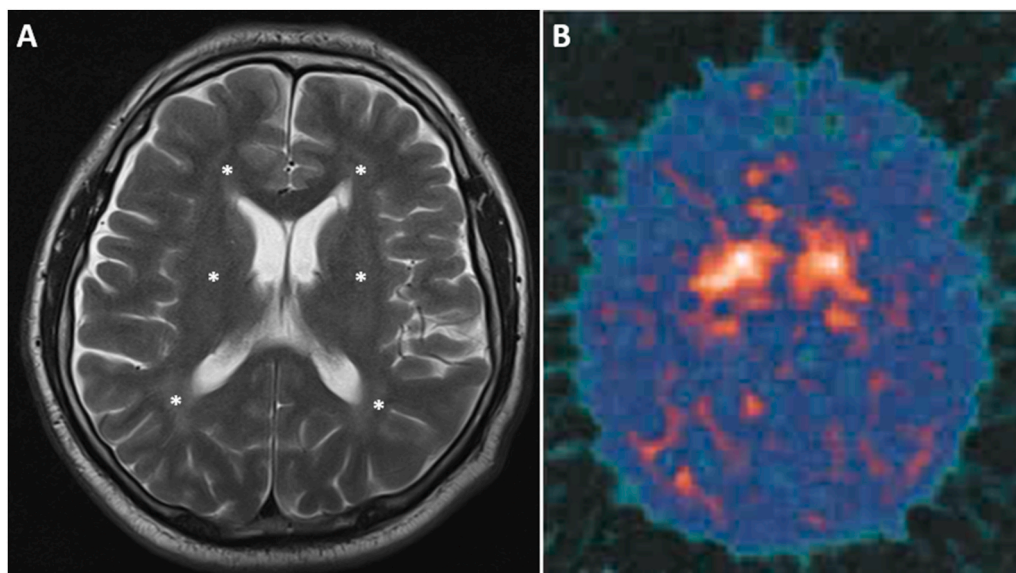
Fig. 1. Illustrative imaging findings of case 26. A. T2-weighted magnetic resonance image shows symmetric white matter hyperintensities (*), typical for phenyl-ketonuria. B. 123I-FP-CIT SPECT (DaTSCAN) depicts left hemisphere dominant decreased tracer uptake in the striatum, particularly in the posterior putamen.

Table 2
Characteristic neurological and neuropsychiatric signs in individuals with late-treated PKU.

Neurological spectrum
Developmental delay (100%)
Movement disorders (77%)
Tremor (38%)
Stereotypies (38%)
Tics (19%)
Parkinsonism (4%)
Limb or gait ataxia (54%)
Seizures (31%)
Brisk reflexes (15%)
Neuropsychiatric spectrum
Intellectual disability (100%)
Restricted language skills (50%)
Obsessive-compulsive behavior (35%)
Self-injurious behavior (31%)
Anxiety (27%)
Aggressive behavior (27%)
Features of autism spectrum disorder (19%)
Depression (19%)

Percentages in brackets refer to the frequency of occurrence in our sample of 26 adult individuals with PKU.

executive functioning are related to dopamine deficiency in the central nervous system [35]. Interestingly, rapid cognitive deterioration has been repeatedly described as a striking symptom in previously undiagnosed adult PKU patients whose symptoms markedly improved with low-phe diet [15,24,36]. Of note, almost half the cases we describe here had severely delayed language development and were not able to establish adequate verbal communication. In early-treated PKU, studies distinctly examining language skills are rare and yield mixed results [37]. Single studies show that most children seem to be less skilled in reading and writing, and adults with early-treated PKU exhibit deficits in language processing [37]. In late-treated PKU, the number of patients with language difficulties relates to the high overall prevalence of intellectual disability. Although some reports have also documented normal or nearly normal intellectually functioning individuals with PKU despite high phe-levels [38,39], the biological causes of such marked differences in outcome as in these exceptional cases currently remain unclear [40].

Obsessive-compulsive behavior was present in 35% of our patients, whereby anxiety and depression were documented in 27% and 19% of cases, respectively. All three disorders have been well-documented in late- and untreated PKU [5,18]. Depletion of monoaminergic neurotransmitters, including serotonin, could explain their presence [41]. Importantly, there is a direct association between neuropsychiatric features and blood phe-levels in people with early-treated PKU [4,42], supporting the notion that continuous metabolic control throughout adulthood is beneficial for the neuropsychiatric outcome.

Finally, almost one third of our patients exhibited self-injurious behavior (SIB). A number of neurometabolic diseases, particularly the ones that involve abnormal dopaminergic metabolism [43], have been associated with the presence of SIB and it has been reported that phe-levels correlate with the intensity of SIB in PKU [43]. In addition, the presence of intellectual disability and restricted behavioral patterns, features which were noted in 19% of our cohort and are commonly encountered in people with ASD, also increase the risk for the presence of SIB [43]. Clinical characteristics, such as those present in people with ASD are 6.1-times more prevalent in PKU compared to the general population [18]. Also, a neurometabolic work-up of patients with ASD led to the diagnosis of PKU in 2.2% of cases [44].

4.3. Therapeutic burden

Until today, a strict low-phe diet, first proposed by Bickel in 1953, remains the cornerstone of PKU treatment. Although extensive dietary restrictions are fundamental to keep blood phe-levels low, they often lead to poor compliance and most often after adolescence, patients fail to follow their diet leading to deterioration of metabolic control [1]. Secondary neurological and neuropsychiatric complications, as the ones we noted above (e.g., case 7) are not uncommon. Further pharmacological treatment options (e.g., pterin supplementation, large neutral amino acids, enzyme therapy) are also available and may allow a higher intake of natural protein [1].

4.4. Limitations

Though 'late' treated is typically meant to refer to patients in whom PKU was detected and treated ≥3 months of age [1], this definition is not always used uniformly [2,9,12] and therefore introduces phenotypic heterogeneity in the range of individuals with PKU labeled as

late-treated cases. We are also aware that beyond the importance of treatment onset, adherence to treatment - particularly throughout the first years of life - is crucial to foster healthier development [6]. For example, we also included three patients (case 5, 12, 14) in our analysis who were diagnosed before the age of 3 months, but in whom dietary treatment was only consistently introduced after the first years of life. In turn, we noted that cases with very late diagnosis and treatment (beyond the age of 7, e.g., cases 3, 8, 16, 17 and 22) had more severe clinical presentations, including movement disorders and neuropsychiatric features, irrespective of their current, well-maintained metabolic control. This further emphasizes the importance of early recognition and consistent treatment.

The availability of brain imaging in our patient cohort was limited (MRI documented in 6 cases). As neuroimaging is only recommended in patients presenting with an unexpected clinical course and/or neurological deficits [1], it was not warranted for medical reasons in most of the individuals we included. Additionally, in the majority of individuals, MRI would not have been feasible due to lack of compliance, such as unwillingness to lie in the scanner, which in many cases was also related to specific phobias. However, we confirm the presence of white matter hyperintensities [7,13,17,33,45] (see Fig. 1A). Even though the correlation of imaging findings with clinical phenotype remains unclear, the extent of white matter lesions appears to correlate with blood phe-levels [46], and MRI changes may be (partly) reversible with strict dietary and metabolic control [17]. Recently, putaminal and thalamic atrophy have been demonstrated in individuals with early-treated PKU [4]. Brain atrophy has also been demonstrated in individuals with late-treated PKU, but systematic studies on this specific topic are scarce [47–49].

5. Conclusions

We here document the neurological and neuropsychiatric symptom spectrum in adults with late-treated PKU. Developmental delay, difficulties in expressive communication, presence of mild ataxia, postural tremor, stereotypies and/or tics, and a history of seizures predominated clinical presentation. Neuropsychiatric features included intellectual disability, obsessive-compulsive and self-injurious behavior, anxiety, depression, and features compatible with ASD. We recommend metabolic testing in individuals in whom a combination of these symptoms and signs might co-occur, and adherence to treatment that might ameliorate the severity of some of these phenotypes even in adulthood.

Authors' roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

TM: 1A, 1B, 1C, 2A, 2B, 3A
JFF: 1B, 1C, 2C, 3B
JH: 1C, 2C, 3B
AKK: 2C, 3B
AJ: 1B, 1C, 2C, 3B
DL: 1B, 1C, 2C, 3B
AM: 1C, 2C, 3B
MS: 1C, 2C, 3B

TJK: 2C, 3B
PF: 1B, 1C, 2C, 3B
AZ: 1B, 1C, 2C, 3B
CG: 1A, 1B, 1C, 2A, 2B, 3A

Declaration of competing interest

The authors disclose no conflicts of interest regarding this manuscript.

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