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Psychiatric disorders in adolescent and young adult patients with phenylketonuria

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ABSTRACT

Background and objectives: Psychiatric symptoms are a challenging aspect in adolescent and adult early treated phenylketonuric (ETPKU) patients. To assess the occurrence of psychiatric disorders we explored the presence of symptoms requiring intervention and further investigated the link between psychiatric disorders, the quality of biochemical control and cognitive functioning.
Patients and methods: Forty-six ETPKU patients (aged 12 to 44) and 30 age-matched healthy controls were subjected to cognitive and psychiatric assessment by means of self-report questionnaires and psychiatric interview. Psychiatric diagnoses, if detected, were made according to DSM-5 criteria. Concomitant IQ, historical and concurrent biochemical metabolic controls were included in the statistical analysis.
Results: Twenty-five out of 46 ETPKUs showed clinical scores on at least one scale of the psychiatric assessment (7/30 in controls); anxiety and withdrawal were the most frequent self-reported symptoms. Seventeen patients (and no controls) met criteria for a psychiatric diagnosis, most of them belonging to the Anxiety Disorders category. The occurrence of psychiatric symptoms was not associated with the life-long and concurrent quality of metabolic control but patients with good metabolic control (≤500 μM) in the first 11 years of life showed higher frequency of psychiatric diagnosis (Fisher's exact p = .0300).
Discussion/conclusion: ETPKUs show a higher than normal vulnerability to psychiatric disorders, which cannot be explained by the usual biochemical alterations influencing intellectual outcome. Our data support the hypothesis that the burden of the disease acts as psychological stress for children and their families. Possible involvement of neuromediators in the pathogenesis of these complex symptoms requires further investigation.

1. Introduction

Phenylketonuria (PKU; OMIM #261600) is an inherited metabolic cause of treatable intellectual disability due to a defect in the phenylalanine hydroxylase enzyme (PAH), which converts phenylalanine (Phe) into tyrosine (Tyr) [1]. Despite the favorable clinical outcome of early-treated PKU (ETPKU) subjects, when compared with late- or untreated patients, a lower Intelligence Quotient (IQ) than expected and minor neuropsychological and psychiatric problems [2–9] remain challenging aspects of the disease.

In ETPKU children and adolescents a higher incidence of the following have been reported: anxiety and depressive symptoms, social isolation, physical complaints, hyperactivity [10–12], attention problems [13–16], low self-esteem, lower achievement motivation and impulsiveness [17].

Among adult PKU patients, depressive mood and anxiety are the most frequently described psychiatric symptoms [18–20], but obsessive-compulsive symptom [8,21], phobia, and panic attacks [22] are also reported. Nevertheless, a clinical characterization of psychiatric symptoms and the link between intellectual development, quality of dietary control and psychiatric disorders, if any, have not been explored so far.

The present study aimed to explore whether ETPKU subjects exhibit an increased psychiatric vulnerability and the possible determining factors.

Abbreviations: ETPKU, early treated phenylketonuria; IQ, intelligence quotient; Phe, phenylalanine; WAIS-R, Wechsler Adult Intelligence Scale-Revised; IDC, Index of Dietary Control.

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2. Materials and methods

2.1. Participants

The sample consisted of 76 subjects (46 ETPKU and 30 healthy controls). Forty-six subjects (29 females, 17 males; mean age = 22.6 years; SD = 7.35; range 12–44 years) were recruited among the PKU patients diagnosed and followed-up at the Department of Paediatrics and Child Neurology and Psychiatry in Rome (Table 1). The inclusion criteria were: a) early diagnosis by neonatal screening program and early treatment; b) genetically confirmed defect of *PAH*; c) age ≥12 years; d) availability of biochemical data covering the patient's history from the diagnosis until the time of the study.

The exclusion criteria included a) intellectual disability (IQ < 75); b) the presence of neurological defects or neurological deterioration (for patients who discontinued the diet).

PKU patients were classified according to plasma Phe concentrations before treatment or under free diet as mild hyperphenylalaninaemia

Table 1
Demographic and clinical characteristics of the PKU sample.

Pt ID	Age (years/ months)	Sex	Genotype	Biochemical phenotype	IDC (μM) ≤ 10 years and 11 months	IDC (μM) > 11 years	Diet (yes/no)	IQ	Onset of psychiatric disorder (years/months)	Psychiatric disorder	School level	Employed
1	16/3	M	p.[Arg176*]; c.[1066-11G>A]	CPKU	451	973	Yes	120	14/0	SP	Hs	NA
2	22/1	M	p.[Arg158Gln]; [Pro281Leu]	CPKU	478	981	Yes	80	19/10	DD	G	Yes
3	20/0	F	p.[Arg158Gln]; [Arg261Gln]	MPKU	290	760	No	103	10/0	SP	Us	NA
4	13/1	M	c.[1066-11 G>A]; p.[Tyr414Cys]	MPKU	313	376	Yes[a]	94	9/6	GAD	Ms	NA
5	18/0	M	p.[Gly325Cys]; c.[1066-11G>A]	HPA	363	626	No	82	9/0	DD	Ms	NA
6	19/0	M	p.[Arg408Gln]; [Arg261Gln]	MPKU	297	565	Yes[a]	114	13/2	GAD	Us	NA
7	16/10	F	p.[Arg408Gln]; [Tyr414Cys]	MPKU	334	512	No	82	6/0	SM	Hs	NA
8	19/3	F	p.[Leu194Pro]; [Arg261Gln]	CPKU	517	1004	No	81	16/3	GAD	G	Yes
9	13/2	M	p.[Leu48Ser]; [Leu369Leu]	MPKU	436	452	Yes[a]	103	11/9	GAD	Ms	NA
10	13/0	F	p. [Arg261Gln]; c.[1066-11G>A]	MPKU	502	684	Yes[a]	84	9/4	GAD	Ms	NA
11	14/0	F	p.[Arg 176*]; [Arg261Gln]	CPKU	421	1033	No	83	9/8	GAD	Ms	NA
12	23/2	F	p.[Arg 243*]; [Arg261Gln]	MPKU	650	735	No	93	18/1	PD	Us	Yes
13	24/5	F	p.[Arg261Gln]; c.[913-7A>G]	CPKU	393	581	Yes	82	23/2	DD	Ud	No
14	35/0	F	p. [Arg261*]; [Asp338Tyr]	CPKU	335	716	No	85	32/0	DD	G	Yes
15	21/3	F	p. [Pro281Leu]; [Pro281Leu]	CPKU	335	956	No	75	12/0	GAD	G	No
16	25/3	F	c.[DEL EX 3]; [1066-11G>A]	CPKU	382	554	No	117	19/0	PD	Us	NA
17	22/1	M	c. [1066-11G>A]; [?]	HPA	396	904	No	85	18/5	PD	Ud	Yes
18	17/9	M	p.[Arg408Trp]; [Arg408Trp]	CPKU	584	911	No	94	–	–	G	No
19	12/4	F	p.[Arg408Trp]; [Arg408Trp]	CPKU	498	764	Yes	84	–	–	Ms	NA
20	18/4	M	c.[1066-11 G>A];p.[Tyr414Cys]	MPKU	358	642	Yes[a]	124	–	–	Us	No
21	18/2	M	p. [Pro281Leu]; [Asp338Tyr]	MPKU	324	648	No	116	–	–	G	Yes
22	13/8	M	p.[Arg158Gln]; [Tyr414Cys]	HPA	346	368	No	84	–	–	Ms	NA
23	13/0	M	p.[Asp59Val]; [Arg261Gln]	MPKU	341	540	Yes[a]	88	–	–	Ms	NA
24	26/0	F	p. [Arg261Gln]; [Arg261Gln]	MPKU	408	648	Yes	86	–	–	Ud	Yes
25	27/6	F	p. [Arg252Trp]; [Arg252Trp]	MPKU	367	661	Yes	112	–	–	G	Yes
26	24/6	F	c. [1066-11G>A]; [?]	MPKU	241	528	No	93	–	–	Us	No
27	23/1	M	p.[Tyr277Cys]; c.[842 + 1G>A]	CPKU	478	477	No	109	–	–	Us	No
28	26/3	F	p.[Tyr277Cys]; c.[842 + 1G>A]	CPKU	599	539.5	No	102	–	–	Ud	Yes
29	22/1	F	c.[441 + 5G>T]; p.[Arg158Gln]	CPKU	567	811	No	88	–	–	G	Yes
30	25/4	F	c.[441 + 5G>T]; p.[Arg158Gln]	CPKU	590	689	No	81	–	–	G	Yes
31	26/5	F	p.[Phe39del]; [Arg111*]	CPKU	604	973	No	91	–	–	Ud	No
32	26/5	F	p.[Arg408Trp]; [Arg408Trp]	CPKU	784	1169	No	90	–	–	Ud	Yes
33	24/0	F	p.[Asp207Ser]; [Pro281Leu]	MPKU	333	460	No	107	–	–	Us	NA
34	24/1	M	p.[Trp187*]; [Trp187*]	CPKU	513	852.5	No	95	–	–	G	Yes
35	25/9	F	p.[Leu48Ser]; [Phe55>Leufs]	MPKU	353	736	Yes[a]	75	–	–	G	Yes
36	28/6	F	p.[Arg243*]; [?]	CPKU	899	1035	No	75	–	–	G	No
37	17/0	F	c.[1066-11G>A]; [?]	HPA	413	822	No	95	–	–	Ms	NA
38	36/2	F	p.[Arg261Gln]; c.[1315 + 1G>A]	HPA	275	363	Yes	75	–	–	G	No
39	12/0	M	p.[Pro281Leu]; c.[Tyr387*]	CPKU	680	1150	No	77	–	–	Ms	NA
40	27/6	M	c.[842 + 1G>A]; [1066-11G>A]	CPKU	804	1455	No	84	–	–	G	Yes
41	29/0	M	p.[Arg158Gln]; c.[1066-11G>A]	CPKU	549.6	1187	No	84	–	–	G	Yes
42	27/0	F	c.[1066-11G>A]; [1066-11G>A]	CPKU	600	1048	Yes	96	–	–	Us	No
43	44/0	F	p.[Phe55Leu]; [Asp338Tyr]	CPKU	260	652	Yes	105	–	–	G	Yes
44	28/2	F	p.[Arg408Trp]; [Arg408Trp]	CPKU	750.3	912.5	No	104	–	–	Us	No
45	32/6	F	p.[Arg408Trp]; [Arg408Trp]	CPKU	668.5	926.5	No	94	–	–	Ud	Yes
46	36/0	F	p.[Pro281Leu]; c.[913-7A>G]	CPKU	778	610	Yes	94	–	–	Us	Yes

Legend: SP: specific phobia; GAD: generalized anxiety disorder; DD: depressive disorder; SM: selective mutism; PD: personality disorder.
IDC: Index of Dietary Control, median value of Phe for the considered period.
Yrs/mo: years/months; NA: not applicable
CPKU: classical PKU (blood Phe at diagnosis or under free diet persistently >1200 μM).
MPKU: mild PKU (blood Phe at diagnosis or under free diet persistently >600 < 1200 μM).
HPA: persistent hyperphenylalaninemia (blood Phe at diagnosis or under free diet persistently >360 < 600 μM).
School level: Ms: middle school; Hs: high school; G: graduate; Us: undergraduate school; Ud: undergraduate degree.
[?] = the mutation on the second allele was not found. MLPA test was negative.
[a] Under Sapropterin treatment (15 mg/kg) since a minimum of 7 years.