The outcome of white matter abnormalities in early treated phenylketonuric patients: A retrospective longitudinal long-term study

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ABSTRACT

Background: Pathogenesis and clinical consequences of white matter abnormalities on magnetic resonance imaging (MRI) in phenylketonuric (PKU) patients are incompletely known.
Objective: To study white matter alterations progression and outcome and its relationships with phenylalanine levels and intelligence quotient (IQ) in early treated PKU subjects who underwent serial MRIs during a prolonged follow-up.
Methods: 47 early treated PKU patients (mean age 25.1 ± 5.6 years; range 12–37 years) have been enrolled when two or more consecutive brain MRIs, a complete biochemical history, and MRI-concurrent blood phenylalanine levels were available. The severity and extension of white matter abnormalities were expressed in a computed score. Consecutive IQ assessments were available in 24 patients. We analyzed intra- and interindividual white matter alterations variations and their relationship with quality of biochemical control and cognitive outcome.
Results: Early treated PKU patients showed a high rate of white matter alterations with a relevant increase in frequency/severity from the second decade of life onwards. Age and quality of dietary control before or between subsequent examinations showed an independent cumulative effect on white matter alterations outcome. No significant association was found between white matter alterations and cognitive outcome. A remarkable interindividual variability was found and several patients disclosed incongruity between the trajectory of white matter alterations and biochemical control. About 30% of white matter alterations variability remains unexplained by the disease-associated determinants.
Conclusions: The evolution of white matter alterations is not significantly affected by intellectual outcome and is affected by aging, chronic exposure to phenylalanine, and unknown individual factors.

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1. Introduction

White matter abnormalities on brain magnetic resonance imaging (MRI) are a common finding in subjects with phenylketonuria (PKU, MIM # 261600) [1]. These abnormalities were initially reported in a few patients suffering from neurological deterioration after low-phenylalanine diet discontinuation and were partially reversed by the reintroduction of a strict dietary regimen [2–5]. Thereafter similar alterations were detected in untreated, late-treated and also in early and continuously treated PKU patients that did not show any neurological symptom [1,6,7]. Curiously, after the few initial cases, no further PKU patients experiencing neurological deterioration have been reported in the literature so far apart from three subjects suffering a progressive visual loss that was reversed by diet restoration (see Rubin et al. 2013 [8], Anwar et 2013 [9] and Leuzzi unpublished case). This is a puzzling aspect considering that the discovery of MRI white matter alterations in PKU patients played a role in favor of the option of diet for life at the end of the '80ies. Major limitations of the available neuroimaging studies are their cross-sectional design and the marked interindividual variability of white matter involvement, which makes difficult to discriminate between disease-associated determinants and individual

Table 1
Demographic data, MRI severity score, biochemical parameters in the presented series of early treated PKU patients.

Patient	Age (years)	Sex	Age at MRI (years)	WMSS	MRI Concurrent Phe (μmol/l)*	IDC (μmol/l)	MRI Concurrent IQ*	Cognitive test
1	27	F	10,4	9	903	631,5	95	WISC-R
			13,3	10	803	757,5	NA	NA
			21,0	10	1495	954	NA	NA
2	24	F	9,4	0	665	581	NA	WPPSI
			12,4	0	787	826	NA	NA
			15	3	961	891	NA	NA
3	20	F	6,6	2	218	188	NA	NA
			14,0	6	899	440	NA	NA
			15,6	13	711	577	98	WISC III
4	21	F	8,4	2	287	451,5	NA	NA
			14,3	17	631	1051	NA	NA
			16,5	4	818	851	45	WISC III
			19,5	4	800,5	1460	50	WAIS-R
5	12	M	7,5	0	200	350	102	WISC III
			10	3	490	411	92	WISC III
6	19	M	14,0	6	435	398	77	WISC III
			16,1	3	616	605	82	WISC III
7	37	M	14,0	6	1094	822,03	NA	NA
			20,5	14	1670	1408,5	NA	NA
			25,4	14	1460	1350	NA	NA
8	24	M	10,0	0	450	495	NA	WISC III
			24,1	12	1900	1700	NA	WISC III
9	24	M	14,0	0	351	334	NA	NA
			22,3	3	682	514	107	WAIS-R
10	28	M	14,4	10	1175	911,5	NA	NA
			20,4	10	727	1049	NA	NA
			23,0	10	810	809,5	NA	NA
			14,4	10	1175	911,5	NA	NA
11	28	F	17,5	4	369	381	NA	NA
			23,2	6	641	495	NA	NA
			26,9	8	977	537	72	WAIS-R
12	20	F	8,0	0	164	278	NA	NA
			14,5	2	1006	380,5	NA	NA
			18,4	4	435	1470	NA	NA
13	19	M	6,4	0	351	171	NA	NA
			13,9	0	722	426	NA	NA
			16,0	10	456	456	112	WISC III
14	27	F	7,8	0	160	786,4	NA	NA
			12,3	0	1649	710,5	NA	NA
			16,7	0	1176	1209	NA	NA
			25,0	2	1352,12	778	90	WAIS-R
15	26	F	20,8	6	148	310	NA	NA
			22,5	7	675	407	NA	NA
16	23	M	13,0	0	239	462	NA	NA
			21,3	4	1080	780	109	WAIS-R
17	26	F	15,0	6	658	631,8	NA	NA
			17,0	0	459	459	NA	NA
			25,1	13	985	994	101	WAIS-R
18	19	M	7,5	0	592	526	NA	NA
			15,3	0	730	673	71	WISC III
			18,0	0	892	700	NA	NA
19	31	F	17,8	8	1768	594	NA	NA
			26,9	9	912	1213	NA	NA
20	32	F	18,8	15	1575	584	NA	NA
			29,7	7	277	1070	NA	NA
21	30	F	16,3	10	950	650	NA	NA
			18,7	10	823	800	NA	NA
			25,0	10	1058	1243,5	NA	NA
			28,5	5	1100	1310	NA	NA
22	27	F	23,4	9	1664	749,5	104	WAIS-R
			27,4	14	701,5	847	NA	NA
23	32	F	27,8	8	1546	763,5	NA	NA
			31,8	6	638,5	815	NA	NA
24	25	F	10,2	0	413	365	NA	NA
			15,0	0	524	463	NA	NA
			20,6	2	476	569,5	NA	NA
			23,0	1	842,5	583	91	WAIS-R
25	24	F	9,1	0	632	621,5	NA	NA
			14,0	0	670	748,5	NA	NA
			15,5	4	519	854	NA	NA
			18,1	4	1150	745,5	NA	NA
			19,2	5	764	772	NA	NA
			21,5	6	985	742,5	93	WAIS-R
			23,3	8	847	772	NA	NA