**Table S1. Reported and previously unreported cases of late-diagnosed (>7 years) PKU patients who have escaped from intellectual disability despite high plasma Phe concentrations**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **Age at diagnosis (M/F)** | **Reason diagnosis** | **Phe (µmol/l)** | **PAH deficiency** | **IQ** | **Neurological** | **Psychological/psychiatric/social** |
| **Normal findings** | **Abnormal findings** | **Normal findings** | **Abnormal findings** |
| 1[12] | 12y (M) | A | 1860 | NR | 851 |  | stiff, clumsy motoric abilities, slightly prostrate posture |  |  |
| 2[13] | 9y,11m (M) | F, hyperacti-vity | 1140-1500 | NR | 1072-1093 | normal reflexes  | EEG abnormal: paroxysmal and disorganized; but poorly organized motor function, which was not improved after institution of diet |  | hyperactive, anxious, extremely excited before any disruption of the routine, considerable perseveration, specific deficit in perceptual visual motor abilities, and poor impulse control |
| 3[14] | 9y (F) | A | 1020-1500 | NR | 953 | normal milestones, neurological examination within normal limits, continued to show normal intellectual capacity despite no institution of treatment |  | good deal of anxiety and inhibition | lack of childhood spontaneity with related ambivalence in acting out her emotional impulses |
| 4[15] | 8y (M) | A | 1680 | NR | 91 |  | ataxia, very mild choreoathetoid-like movements which could be from irritable restlessness and poor coordination, slight difficulty in speech which was attributed to poor tongue coordination, some slowness in reading |  | nervousness |
| 5[16, 17] | 8y (M) | A | 1560 | NR | 892 | NR | NR | NR | NR |
| 6[18, 19] | 36y (F) | B | 1236-1248 | NR | 1024 | NR | mild reading disability | NR | NR |
| 7[20] | 12y (M) | A | 1200-1500 | NR | 91-100 | NR | NR | NR | NR |
| 8[21] | 12y (F) | A | 1920 | NR | 106 | no abnormalities on neurological examination; EEG borderline normal |  | bright, quiet and confident |  |
| 9[22] | 26y (F) | F,high Phe in child without enzymatic defect | 1200-1800 | NR | 964 | NR | NR | NR | NR |
| 10[23] | 29y (F) | B | 1020-1320 | NR | ≥904 | no neurological abnormalities on examination  | EEG: mildly abnormal paroxysmal record; very brisk tendon reflexes | NR | NR |
| 11[24] | 34y (F) | C | 1320-1560 | NR | 974 | NR | NR | NR | NR |
| 12[24] | adult (F) | C,E | 1560-1680 | NR | 922 |  | did not begin talking as early as her brother | NR | NR |
| 13[25] | 32y (F) | B | 1302-1560 | NR | 882 | no seizures | EEG low voltage, diffuse slowing, and paroxysmal generalized high voltage | no psychic disturbances |  |
| 14[26] | adult (F)  | B,C | 1500-2580 | NR | 84-904 | no abnormalities on neurological examination, EEG normal |  | very apt in nursing her three invalid children, coped well with family illnesses |  |
| 15[10] | 7y,4m (F) | A | 1560 | NR | 1046-982 | NR |  | NR | NR |
| 16[27] | 8y (M) | A | 1080-1320 | NR | 933 | EEG normal |  | NR | NR |
| 17[27] | 12y (F) | A | 960-1200 | NR | 913 | EEG normal |  | NR | NR |
| 18[27] | 68y (M) | F, survey in hospital | 1200-1500 | NR | >80 | developed normally until 2 years  | when he suffered from meningitis, thereafter he required 6 months to recover normal motor function but was considered intellectually retarded |  | admitted to sheltered environment after having been convicted for which he was considered innocent |
| 19[28, 29] | 29y (F) | B | 1560-1860 | NR | \* | NR | NR | NR | NR |
| 20[30, 31] | 28y (M) | A | 1370-1510 | NR | 1203-1322 | no seizures, no other neurological abnormalities | EEG mild temporal dysrhythmia | NR | NR |
| 21[32] | 11y (M) | A | 1200 | NR | 1045 | NR | NR |  | very tense and anxious and defends against this by clowning, pressure of talk, and a rather uninhibited call for reassurance |
| 22[17, 33] | 9y (F) | A | 1500 | NR | \* | no abnormalities on neurological examination |  |  | nervy, fearful, and easily upset at 11 years, and a little tense at 17 years |
| 23[17] | >12y (M) | A | 1260 | NR | \* |  | microcephaly, slight fine tremor both hands, bilateral patellar clonus |  | immature, considerable abnormality with respect to his adjustment, neuropsychological subtest scores indicate emotional disturbance rather than the effect of brain damage, some difficulties with non-verbal abilities |
| 24[34] | adult (M) | D | 1332 | NR | 100 | NR | NR | NR | NR |
| 25[35] | 19y (F) | D | 1939 | NR | 122 | NR | NR | NR | NR |
| 26[35] | adolescence (F) | A | 1735 | NR | \* | NR | NR | NR | NR |
| 27[35] | 24y (F) | D | 2655 | NR | 86 | NR | NR | NR | NR |
| 28[36] | 22y (F) | D |  | NR | 934 | EEG within normal limits | hyperactive tendon reflexes, downgoing plantar reflexes | NR | NR |
| 29[37] | 28y (F) | B,C | 1200 | NR | 896 | NR | NR | Inconspicuous |  |
| 30[38] | 27y (F) | D | 1340 | NR | 924 | NR | NR | NR | NR |
| 31[11] | 21y (F) | A | 1500-1700 | NR | 824 | normal muscle coordination (won open art competition) |  | NR | NR |
| 32[39] | adult (F) | NR | 1520 | NR | 97 | NR | NR | NR | NR |
| 33[40] | 35y (F) | C | 1374 | NR | 1077 | NR | NR | held responsible job |  |
| 34[40] | 64y (F) | C | 1588 | NR | 8510 | NR | NR | held responsible job |  |
| 35[41] | adult (F) | C | 2100 | NR | \* | NR | NR | NR | NR |
| 36[42] | 23y (F) | A,C | 1346 | Yes | \* | NR | NR | socially well adjusted, very little suggested PKU in her behavior |  |
| 37[42] | 24y (F) | C | 1265 | Yes | \* | NR | NR | socially well adjusted, very little suggested PKU in her behavior |  |
| 38[43] | 22y (F) | C | 1423-1643 | NR | \* | NR | NR | no social and behavioural problems |  |
| 39[44] | adult (F) | B,C | 1200 | Yes | 100 | NR | NR | socially well adjusted, works as school teacher |  |
| 40[45] | adult (F) | C | >1200 | Yes | \* | NR | NR | NR | NR |
| 41[46] | 11y (M) | F, tremor | *1740* | NR | *106*5 | *no history of seizures. EEG: no abnormalities No abnormalities on cerebral CT.*  | *from 9y: distal upper limb tremor (shaking hands), dysgraphy, problems in fine motor skills, worsening school performances. At 17y: dysmetabolic leukoencephalopathy with anterior and posterior periventricular white matter abnormalities on MRI* | *high school graduate* | *irritability* |
| 42[46] | 18.4y (F) | F,amaurosis fugax | 1500-1550 | NR | 85 |  | squint and amaurosis of the left eye, white matter involvement score 8, learning difficulties | NR | NR |
| 43[47-49] | 24y (F) | C | 1210-1800 | Yes | 1004 |  | only mild changes on MRI confined to parieto-occipital region  | NR | NR |
| 44[47, 48] | NR (F) | NR | 1200 | Yes | 1054 |  | only mild changes on MRI confined to parieto-occipital region  | NR | NR |
| 45[50] | 32y (F) | A,C | 1745 | Yes | 92 | NR | NR | NR | NR |
| 46[50] | 21y (F) | C | 1273 | NR | \* | NR | NR | NR | NR |
| 47[50] | 25y (F) | C | 1739 | Yes | 100 | NR | NR | NR | NR |
| 48[50] | 20y (F) | D | 1376 | NR | 105 | NR | NR | NR | NR |
| 49[51] | adult (F) | C | 1380 | NR | 904 | no PKU phenotype |  | no PKU phenotype |  |
| 50[52] | NR | A | 1274 | Yes | >856 | NR | NR | NR | NR |
| 51[52] | NR | A | 1470 | Yes | >856 | NR | NR | NR | NR |
| 52[53] | 57y (F) | F,progres-sive spastic parapare-sis and dementia | 1862-2153 | Yes | 108 | normal neurodevelopmental history, normal visual and somatosensory evoked potentials, on MRI no white matter abnormalities | since some years progressive spastic paraparesis and dementia, brisk reflexes, ankle clonus, upgoing left toe |  | never employment/ driving licence/ dated/married, now flattened affect, marked psychomotor slowing |
| 53[54] | adult (F) | D | >1200 | NR | >80 | NR | NR | NR | NR |
| 54[54] | adult (F) | D | >1200 | NR | >80 | NR | NR | NR | NR |
| 55[54] | adult (F) | D | >1200 | NR | >80 | NR | NR | NR | NR |
| 56[54] | adult (F) | D | >1200 | NR | >80 | NR | NR | NR | NR |
| 57[55] | adult (F) | C | 731-1232 | Yes | \* | NR | NR | NR | NR |
| 58[56] | adult (F) | C | 1560 | Yes | \* | NR | NR | NR | NR |
| 59[57] | adult (F) | B | 850-1300 | Yes  | *87*8 |  | tremor |  | *some problems in executive functioning: difficulty planning, reduced working memory, difficulty dividing attention, and* attention deficit, hyperactivity |

NR: not reported; A: PKU sibling; B: PKU offspring; C: affected offspring; D: screening; E: PKU relative; F: other

IQ assessment by: 1 Binet-Simon-Kramer; 2 Stanford-Binet; 3 WISC; 4 WAIS; 5 Terman-Merrill; 6 Hawik-Test; 7 Raven’s Standard Progressive Matrices; 8 Merill-Palmer Scale; 9 Witti; 10 estimated; \*reported to have a “normal intelligence”

Additional Information provided by the physicians/treating centers of previously described cases is stated in italics.