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# Undiagnosed/Untreated Phenylketonuria (PKU) With Normal IQ and the Possible Role of Magnetic Resonance Spectroscopy (MRS)/Correlated Spectroscopy (COSY)

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## Abstract

As an addition to the recent papers by van Vliet et al. we have extracted a number of individuals, derived from the older literature, bibliographies and "personal communication", reporting untreated, (usually classical), phenylketonuria with normal IQ. We have pointed out that a number of these patients develop serious neurological deterioration in early to mid-adulthood, some not responsive to dietary (phenylalanine restriction) treatment. Magnetic Resonance Spectroscopy (MRS) studies suggest that low levels of brain phenylalanine may be a possible answer-perhaps due to a modifier gene but the aging brain may later become more susceptible. Quite a number prominent research centers around to world have been unable to reproduce the MRS data supporting this hypothesis.

**Keywords:** Phenylketonuria (PKU); Phenylalanine; Classical PKU; Untreated PKU; Magnetic resonance spectroscopy; Correlated spectroscopy.

**Abbreviations:** NBS: New Born Screening; PKU: Phenylketonuria; Phe: Phenylalanine; MPKUS: Maternal Phenylketonuria Syndrome; MR: Mental Retardation; MHP: Mild Hypephylalanemia; CHD: Congenital Heart Disease; IUGR: Intra Uterine Growth Reduction; IQ: Intelligence Quotient; MRS: Magnetic Resonance Spectroscopy; MVA: Motor Vehicle Accident; COSY: Correlated Spectroscopy; Tyr: Tyrosine; BH4: Tetrahydrobiopterin.

## Introduction

The incidence of normal IQ in untreated classical PKU has, traditionally, been assessed at 1%-2% [1,2]. This claim is based, in retrospect, on faulty "selection biased" surveys in the 1950's to the 1970's, of institutions for the retarded [3-6]. This mantra has been questioned over the years [7,8] and claims of a frequency of up to 20% have been made [9]. A recent systemic review by van Vliet et al. from van Spronsen's center [10,11], with detailed inclusion criteria (*i.e.*: (1) PKU diagnosis and treatment after 7 years of age. (2) Untreated plasma phe>1200 µmol/L (classical PKU). (3) IQ ≥ 80 found 59 published cases of untreated classical PKU with normal/low normal IQ's (though "at least 19 of these showed other neurological, psychological and/or behavioral symptoms.").

## Patients

### Patients born pre-universal New Born Screening (NBS)

1. "Proceedings" of a conference "phenylketonuria and allied metabolic diseases" held in Washington, DC, April 6-8, 1966 [12] unearthed several cases of interest:

- Bessman describes a family of 4, all males. Three had PKU (all untreated). The youngest, diagnosed at age 4 years, IQ 55. The other 2, aged 9 years and 13 years, IQ's 90-97 and 93-99. All 3 had blood phenylalanine (phe) levels between 1200-1800 µmol/L.
- Woolf quotes Laurance B-monozygotic male twins, diagnosed at age 11 months, one IQ 55, blood phe 1576-3376 µmol/L, the other, IQ 100, blood phe 1575-2485 µmol/L.
- Guthrie in discussion of BJ White's presentation quotes "Dennison in Pennsylvania" reporting an untreated "PKU woman with normal IQ who produced two offspring with MPKUS embryopathy".
- Cooper quotes Jervis, "at the Rosewood seminar" citing two untreated phenylketonuric sibs, one of whom was an "imbecile" (IQ 30-50) and the other "an Oxford University student".

2. Phenylketonuria 1963. Editor-Frank L Lyman [13].

- Jervis GA cites Coates S et al reporting a case of PKU with normal IQ (above 100) with Gower's muscular dystrophy.
- Jervis also describes ("personal observation") two untreated PKU sibs with IQ's of 100 and 20 and "similar" blood phe levels.

In the chapter by Bickel et al. one of the tables quotes Gruter (Gruter die beseutung des phenylalanine stoffwechsel fur die hirnfunktion. Habllitationsschrift Unversitat Marburg 1960), describing an untreated 8.3 year old with an IQ of 90 (in German, no english abstract available).

In the bibliography 9 cases of normal IQ in untreated PKU are cited: i) Cowie VA. Atypical case of Phenylketonuria. ii) Hsai et al. A case of PKU with borderline intelligence iii) Sutherland BS et al. A syndrome of PKU with normal intelligence and behavior disturbances iv) Partington MW [5] presents a mother with untreated classical PKU and an IQ of 102 who had 3 offspring, 2 with PKU and one non-PKU (IQ 103). v) Tischler et al. vi) Woolf et al. atypical phenylketonuria in sisters with normal offspring. vii) Tapia Phenylpyruvic Oligophrenia. Report of a case with normal intelligence.

3. Hsai [14] Phenylketonuria and its Variants in: Progress in Medical Genetics. Volume VII. 1970-reviews data on 11 non-PKU offspring of 9 women with "hyperphenylalaninemia" (phe elevated but <909 µmol/L) and found all had normal IQ's[14].

4. Primrose [15] describes a single untreated classical PKU patient of low normal IQ (82) with a profoundly retarded PKU sibling. A "literature review" by this author unearthed "6 similar families".

5. Schovenko et al. [16] reports "a case of untreated classical PKU with average IQ" (in German-no abstract available).

6. Levy et al. [7-8] testing 453,118 randomly chosen umbilical cord bloods found 22 previously undiagnosed subjects with PKU: 2 had classical PKU, one with an IQ of 94.

7. Perry et al. [17] describe 4 adult siblings with previously unrecognized and untreated PKU. Three had normal intelligence (IQ's 95-106) and one had low normal IQ (83)-one of the 3 was a university graduate. All 4 sibs had blood phe levels of 848-1030 µmol/L (Mild/Atypical PKU values). Three PKU women in this sibship gave birth to 9 non-PKU children, all of whom had varying degrees of intellectual deficit. Two of these female sibs went on to develop psychotic episodes resulting admissions to psychiatric facilities.

8. Allen et al. [18] describe a 10 year old boy assessed by psychiatry because of hyperactivity and disruptive class behavior. Neurological exam was unremarkable. His IQ was 107. A paternal aunt and uncle were institutionalized with PKU (phe's 1212.1 and 1248.3 µmol/L and IQ's 50 and 62 respectively). This boy's phe was found to be 1212.1 µmol/L. A 7 months trial of phe restricted diet showed no change. He was diagnosed as "chronic brain syndrome".

9. In 1957 Bickel et al. [19] reported 2 untreated classical PKU girls with normal IQ's.

10. In 1963 Mabry et al. [20] describe 2 untreated sisters with PKU (the first initially diagnosed by routine urine/diaper ferric chloride test) who had IQ's of 121 and 113 and phe values of 1018-1212 and 848-1109 µmol/L respectively. They had no school or behaviour problems.

11. In 1963 Zinger [21] reported two children in Czechoslovkaia with untreated PKU and normal intelligence.

12. In 1958 Leonard et al. [22] describe an 8.5 years old female with "borderline/normal" IQ (70-80) and a serum phe of 2212 µmol/L. Family stress in early infancy may have delayed her early development (abusive father).

## Post-NBS literature

In the "developed" countries universal New Born Screening (NBS) started, for the most part, between 1965 and 1978 (although this, at present, only covers about 15% of the world's newborns) [23]. Since then, therefore, virtually all PKU positive NBS patients have been treated-eliminating the "normal IQ, untreated group" from detection in these jurisdictions. There have been, however, three interesting reports of older (unscreened) sibs of patients diagnosed in the early post-NBS days.

13. Hsai [14] in a table attribute to Berman (1969) [24] listing 27 early treated, NBS diagnosed, PKU patients (mean IQ 98) vs. 31 late treated or not treated older sibs (mean IQ 70)-however 6 of this latter group (20%) had normal IQ's.

14. Koch [25] in 1971, tested all of the unscreened older siblings of PKU neonates diagnosed in his center in the early days of NBS and found 15 with undiagnosed/untreated PKU-3 (20%) had normal IQ's.

15. Machill et al. [9] screened 233,633 pregnant women in East Germany for PKU between 1972 and 1989 and found 17 women with previously undiagnosed PKU and normal IQ. After deft manipulation of his data he concluded that 20% of untreated subjects with Classical PKU have normal IQ's.

16. Campistol et al. [26] reviews 121 PKU patients in Spain (age 1 months to 46 years)-71% diagnosed by NBS and 28% "late diagnosis". 7% of the late diagnosis group had normal IQ (95.3% of the NBS group had normal IQ).

## Patients diagnosed and treated early but diet was discontinued in mid-childhood

Thompson et al. [27] reported 7 young PKU adults in the UK diagnosed by NBS, but phe restricted diet had been discontinued in mid-childhood. They developed serious neurological diseases (Para paresis, quadriplegia, ataxia, dystonia, seizures, and tremor) in early adulthood. Only 2 improved with re-institution of dietary therapy.

Seki et al. [28] reported a 48 year old Japanese woman diagnosed at 6 years of age with classical PKU and was treated with a low phe diet 'till age 15. She was "mildly mentally retarded but was able to conduct her daily life without any help." At age 48 she developed severe neurological symptoms including loss of speech, spastic paraplegia, severe disturbance of consciousness and hyperhidrosis. Her serum phe was 1212 µmol/L. Dietary therapy was restarted with very gradual, but incomplete improvement.

## Diagnosed late only as a result of Maternal PKU embryopathy (MPKU) in an offspring

In post-1990 world literature reviews Hanley et al. [29-31] we unearthed reports of 60 women with undiagnosed (mostly classical) PKU with probable normal or near normal IQ's who were diagnosed only because they produced 119 offspring with "MPKU embryopathy" (microcephaly, MR, IUGR, CHD, facial dysmorphology). The most notable group was from NSW Australia, where 18 women were diagnosed with PKU only after having given birth to an abnormal child [32].

## Reports of late neurological/cognitive decline (mid-adulthood) in previously normally functioning undiagnosed/untreated classical PKU patients

- Male, functioning normally 'till age 32. Then developed spastic paraparesis and dementia (IQ dropped to 68). Phe 1663 µmol/L. BH4 normal. No response to phe restricted diet [33].
- Adult woman functioning normally 'till age 57 with an IQ of 108. Then developed slowly progressive spastic paraparesis and dementia. Blood phe was 2155 µmol/L. There was "partial improvement" on phe restricted diet. Male sibling has PKU-and was mentally retarded but neurologically intact [34].
- Forty-five year old female, previously undiagnosed, developed sudden progressive neurological deterioration-spastic tetraparesis, ataxia, tremor, cognitive deterioration, disorientation and concentration problems. She had abnormal EEG, MEP and MRI. Her IQ was 95. phe was 882 µmol/L was placed on low phe diet with good blood levels and "almost complete recovery" within 6 months [35].
- Forty-five year old male. He was a high functioning, successful business man. But began having neurological symptoms including seizures (one leading to a serious MVA). He had been drinking copious amounts of "diet coke". He "googled" aspartame and asked his neurologist to measure his phe level-it was 4500 µmol/L (dropped to 3500 µmol/L off aspartame). Subsequently lost to follow-up. (Adams J. personal communication.)

- Daelman et al. [36] report a 33 year old, diagnosed with PKU only after presenting with sudden onset of spastic paraparesis, dementia and parkinsonism. They report a further 4 adults (33-45 years of age), treated in childhood, but whose diet had been discontinued ± 10.5 years prior. They also developed neurological signs but most responded to re-introduction/introduction of diet. All had blood phe levels of >1500 µmol/L.

## Some "Clues"

A detailed survey in the UK Murphy et al. [37] in 2008 searching for undiagnosed/unreported adults with PKU expected to find 2,000 (based on the known UK, post universal NBS screening, PKU prevalence of 1:8,000) unearthed only 98. This may have been a faulty survey method, the presence of variants (mild/atypical PKU and MHP)-which make up 30%-50% of cases or large numbers of intellectual challenged adults never tested for PKU. But the possibility remains that some untreated, unscreened adults with PKU may have relatively normal intellectual function. After all, epidemiologists and bioethicists continue to remind us that no statistically valid, randomized, placebo controlled, studies on PKU newborn screening [38] or treatment [39] have ever been carried out.

Estimated incidence of PKU prior to universal NBS (based mostly on extrapolation from PKU patients found in large institutions for the retarded 1%-2% of whom had PKU) for example, varied from 1:25,000 in the USA Jervis [40] and 1:15,000 in the UK and Northern Europe (see summary by Partington) [41]. Since universal NBS began, however, the incidence has been found in these jurisdictions, to be 1:15,000 and 1:8,000 respectively.

## Anecdotal/Personal Observation, Unpublished, Information

In 1984 we carried out dried blood spot testing for PKU on 10,000 randomly chosen lab samples in our Ontario (Canada) central provincial lab (unpublished) similar to Levy's [7] study and to our surprise, found 2 middle age adult males with previously undetected classical PKU.

One lived 100 km from our center. Our psychologist C Netly, travelled to this individual's home and carried out an IQ test. It was 108. The second was a member of the world renowned RCMP (Royal Canadian Mounted Police). We were reluctant to request an IQ test but presumed it would be normal.

In 34 years as director of the PKU programme at our center i was involved in treating about 200 patients. A few stood out as "unusual". One family with 3 classical PKU children, diagnosed by NBS, was notoriously non-compliant-missing appointments, not regularly mailing in dried blood spots, not following dietitian/nutritionist's instructions and phe levels were frequently high.

However all 3 had high normal IQ's and were excellent students. Another male diagnosed by NBS started treatment early and blood phe levels were always within target range, but IQ test results gradually declined to "moderately retarded" levels. Tetrahydrobiopterin (BH4) testing was normal. A third a female with highly intelligent parents diagnosed by NBS, treated early with excellent phe levels but ended up with a severe learning disability. One wonders if these findings are all related to PKU.

## Magnetic Resonance Spectroscopy (MRS)/Correlated Spectroscopy (COSY)

A method suited for noninvasive determination of various cerebral metabolites (including phenylalanine and tyrosine) *in-vivo* NMR spectroscopy (MRS) [42] was utilized by Weglage et al. [43], to report 4 patients with untreated classical PKU - 2 with normal IQ's (100 and 105) and 2 profoundly retarded. All 4 had blood phe levels of 1200-1500 µmol/L. The 2 normal IQ patients had low brain phe levels while the 2 retarded patients had high brain phe levels. This was originally thought to be a major break-through (perhaps a modifier gene [44]) explaining the variations reported above. The Los Angeles group Moats et al. [45] carried out MRS studies in 21 PKU subjects and while seeming to have some problems sorting out their findings, did feature 4 "exceptional" classical PKU adults with high IQ's despite having been off diet since childhood, who had "remarkably low" brain phe. Leuzzi et al. [46] in Italy examined 10 off-diet PKU adults and found 2 with discrepant blood and brain phe values. One, a late detected patient with normal mental development and a high level of plasma phe but a "relatively low" concentration of brain phe. The other, a late detected subject with severe neurological impairment and a very high level of brain phe but plasma phe was compatible with a diagnosis of mild/atypical PKU.

Bik-Multanowski et al. [47] in Poland after several failed attempts, examined 39 PKU adults by MRS; 28 had abnormal neuropsychological tests but 2 (7.1%) had normal IQ testing and low brain phe. However (*via* the "grape vine") clinicians in numerous other centers around the world have had trouble reproducing the results of these researchers in Germany Italy, Poland and more recently Turkey [48]. Waisbren et al. [49] in Boston now describe a pilot study to examine the potential of a new variation of MRS, "Correlated Spectroscopy (COSY)", to "non-invasively quantify brain phe and Tyrosine (TYR) and explain variability in neuropsychological functioning". They tested 9 early diagnosed classical PKU adults. Associations were in the "expected direction" with higher brain phe and lower brain TYR related to poorer functioning. Further validation studies are planned.

## Discussion

It has been recognized for some years that simple IQ testing alone may be too "blunt" for long-term assessment of PKU patients and that more complex neurocognitive psychological testing is necessary to tell a more complete story [50-53]. In addition neurological and psychiatric problems arose as patients aged [54,55]. The earlier literature, reviewed here, usually focused on IQ testing alone. It has now become obvious that more in depth approaches are necessary to find (in some instances) more subtle but significant, changes in brain function. There are, for example, few detailed records of eventual IQ's in untreated milder forms of PKU ("mild/atypical PKU" and "non-PKU Mild Hyper Phenylalaninemia (MHP)" phe blood level on unrestricted diet 600-1200 µmol/L and 200-600 µmol/L respectively). Waisbren et al. [8], for example, found 11 patients with previously undiagnosed Mild/Atypical PKU (mean IQ 97.3) and 9 with MHP (mean IQ 105.7).

It would appear, therefore, that the incidence of normal IQ in untreated classical PKU could possibly be as high as 20% and this may be related to differences in brain vs. blood phe levels. However, at least some of these individuals may undergo changes as their brain "ages" causing the previously low brain phe values to change and

suddenly result in major, sometimes devastating, often irreversible, alterations in function. If the present roadblock in reliable non-invasive methods of measuring brain phe and TYR can be solved this might be very useful, with perhaps regular (annually) MRS testing as part of the follow-up protocol for PKU. The publication by Waisbren et al. [49] is showing signs of progress. Some of these individuals may not need phenylalanine-restriction at least in the early years but follow-up is crucial.

There is a small overlap here (3 cases) in reports presented in van Vliet et al. [10] review and this paper but these were included because of our inclusion of interesting narratives about how the diagnoses were made.

In a very recent publication Bik-Multanowski et al. [56] suggests that a defect in the LAT1 amino-acid transporter may alter brain phe content and suggests that this should be examined further.

## Conclusion

Admittedly many of the reports in this paper are incomplete, poorly documented hearsay anecdotal include mild variants and are non-specific. However they do suggest that more numbers than suspected are a possibility.

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