Reinstitution of Diet Therapy in PKU Patients from Twenty-two US Clinics

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Abstract: In a nationwide survey we found 72 PKU (phenylketonuria) patients who had terminated diet but later returned to diet. Sixty-one patients resumed diet due to clinical problems. Age at initial diet discontinuation ranged from three to 20 years. The most prevalent problems reported were poor school performance, and mood and/or behavior changes. Following diet reinstitution, only positive changes were noted for 42 patients, no changes for 19 patients, and 11 had one or more negative changes. Improvements and blood phenylalanine levels were not significantly correlated, but only 11 patients maintained levels < 10 mg/dl. The number of improvements was significantly correlated with length of time on diet ($p < 0.001$). After a median of 10 months on diet, 22 patients had again discontinued due to poor diet control, lack of motivation, poor formula tolerance, lack of apparent benefits and/or changes for the worse. Median time on diet for the 50 second-time continuers was two years nine months. (*Am J Public Health* 1985; 75:39–42.)

Introduction

Prior to 1977 there were limited reports of unfavorable responses to discontinuation of diet therapy in phenylketonuria (PKU). These reports were concerned primarily with late-treated patients or with those whose diets were discontinued before the age of five years.[1] Since then, unfavorable effects of diet discontinuation in early-treated patients have been described.[2–5] Such reports have prompted a change in the policies of PKU clinics regarding diet discontinuation;[6,7] the majority of clinics now recommend indefinite continuation of diet.[7]

Some clinics have tried reinstitution of the phenylalanine-restricted diet. In 1969, Murphy described diet reinstitution for two early-treated PKU siblings.[8] In a 1978 survey of PKU clinics in the US,[6] 16 patients had been returned to a restricted-phenylalanine diet but no additional information was available about them.

The present investigation was undertaken to describe a larger population of patients who have been returned to the PKU diet, the reasons for diet reinstitution, the success or failure of these patients in maintaining diet a second time, and the problems or improvements reported after diet reinstitution.

Methods

In a 1982 survey done for the US Department of Health and Human Services, Bureau of Community Health Services, a questionnaire requesting PKU patient population data was sent to all previously identified programs involved in the treatment of PKU in the United States. We identified 109 clinics or health departments which coordinate PKU treatment.[9] Follow-up questionnaires were sent to the 42 clinics for which responses indicated possible experience with diet reinstitution.

For each patient, general descriptive information was requested along with an indication of whether or not any of a series of defined clinical problems occurred while the patient was off diet, and an indication of whether or not any of a series of defined clinical problems or improvements had occurred after diet reinstitution. In addition to a response of "yes", "no", or "no data", comments were requested regarding each problem or improvement.

The questionnaire was completed during June-October 1982 by the program director, nutritionist, or nurse familiar with the patient population. All reports were based on clinic staff observation or interpretation of clinical data, or observation by parents or school personnel as described to clinic staff. Clarification and missing data were obtained by telephone in 1983.

Results

Data were received on 97 patients; however, two patients had not previously been on diet, six had never been off-diet, two had mild hyperphenylalaninemia rather than PKU, four females were returned to diet for pregnancy only, and insufficient data were available on 11.

This paper presents data from 22 clinics following 72 patients (36 males, 36 females) who were returned to the phenylalanine-restricted diet after a period of being on a free diet. Almost all patients except for the moderately/severely retarded had been on the diet since early infancy. Thirty of the patients (15 males, 15 females) were reported to have normal intelligence (IQ > 85), 33 patients (16 males, 17 females) were borderline or mildly retarded, and nine patients (five males, four females) were moderately or severely retarded. The decision to reinstitute diet appears to be unrelated to sex or IQ.

Sixty-one of the patients were returned to the diet due to clinical problems; nine were returned on the basis of literature reports of adverse consequences of diet discontinuation. For two patients, the reason was not given. About one-half of the subjects were returned to diet at the request of the clinic. The decision was made by families for the majority of the others.

The majority (48 patients) consumed Phenyl-Free formula (Mead Johnson); others (19 patients) took Lofenalac (Mead Johnson) or a mixture of PhenylFree and Lofenalac (one patient). Four patients were considered to be "on diet" despite no intake of formula. There were wide variations in the percent of dietary protein provided by formula, and similar wide variability in the reported average intake of phenylalanine by the patients.

Twenty-two patients discontinued diet a second time, while 50 patients remained on diet at the time of the survey. One clinic indicated that data were provided only for patients who continued diet a second time. The median age for initial diet discontinuation was between six and 6 1/2 years

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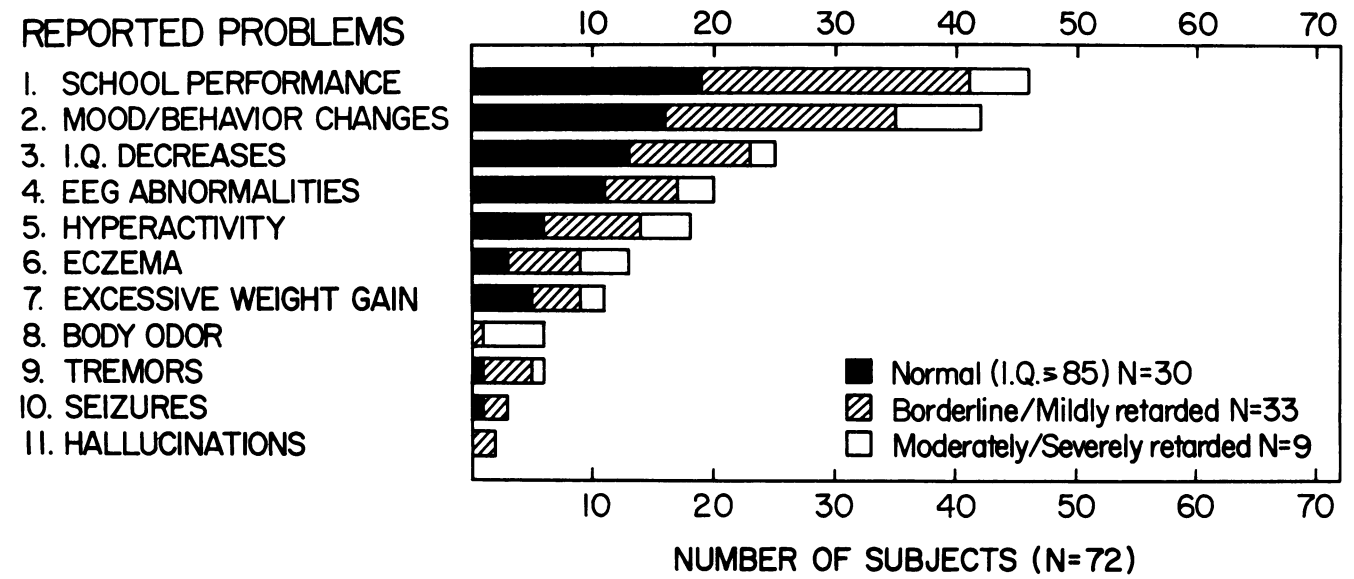

FIGURE 1—Off-diet Problems of PKU Patients (empty spaces indicate the numbers of patients not reported to have problems)

for all groups except the very small number of moderately/severely retarded females.

No age predominated for reinstitution of diet for patients with IQs less than 85. For the normal IQ group, 18 patients were returned to diet at elementary school age (six–11 years), four at middle school age (11–14 years), two at preschool/kindergarten age (3 1/2 to six years), two were young adults (> 19 years), and one was high school age (15 years).

The median time interval between diet discontinuation and diet reinstitution was considerably shorter (two years four months) for the group of patients with normal intelligence than for the other groups (four years six months to six years eight months), but variability was great.

Figure 1 shows that the most prevalent problem reported for patients at all three cognitive levels while off the phenylalanine-restricted diet was poor school performance. Mood or behavior changes were more common for males (19 patients) than for females (11 patients), and more males had multiple behavior problems. In the normal IQ group, mood or behavior changes were reported for nine of 15 males and six of 15 females.* Many clinics did not report actual off-diet IQ scores; those who did so, reported decreases of five to 25 IQ points on standardized IQ tests. Decreases occurred in all IQ groups.

There was no significant correlation between number of observed problems off-diet, and either age of patient at time of diet discontinuation, or length of time off-diet.

Figure 2 shows both the reported positive and negative results of diet reinstitution for the patients by cognitive level. Some of the improvements were noted to be minimal, while others were called "dramatic" or "very significant." The time when these changes occurred was not reported for most subjects. Only positive changes were noted for 42 patients, no changes for 19 patients, and 11 had one or more negative changes.

*Including depression or more frequent crying (four males, three females), hyperactivity (four males, three females), irritability or tantrums (four males); and impulsive, disruptive or bizarre behaviors (four males).

Figure 3 shows the mean plasma phenylalanine levels reported following diet reinstitution. The levels achieved were higher than the stated clinic goals in most cases. No data were obtained on general dietary control prior to initial diet discontinuation.

Average blood phenylalanine levels after diet reinstitution were compared with the four areas in which the greatest number of off-diet changes were noted (school reports, mood, IQ, and electroencephalogram). One point was allotted for each reported improvement, and minus one was allotted for each area that worsened. No significant correlation was found between blood phenylalanine levels obtained after diet reinstitution and number of areas improved ($r = 0.074$, $p > 0.5$ for 30 males and $r = 0.213$, $p > 0.3$ for 32 females). The mean number of improvements was 1.03 for males and 1.24 for females. A number of patients reportedly improved in one or more areas when plasma phenylalanine levels were in the 20–25 mg/dl range.

The number of improvements in the areas of school reports, mood, IQ, and EEG was significantly related to the length of time the patients had again been on diet ($r = 0.483$, $n = 64$, $p < 0.001$). No significant correlation was found between number of improvements and age at time of diet reinstitution.

Eczema was eliminated by diet reinstitution in all but one patient, who improved only temporarily. Average blood phenylalanine levels of 15 mg/dl were adequate to curb eczema in these patients. For some patients, eczema was eliminated when average blood phenylalanine was higher than 15 mg/dl.

For patients who discontinued diet a second time, reasons cited were poor dietary control, poor tolerance of formula, lack of motivation by parents and/or the patient, and lack of apparent improvements. Discontinuation or continuation of diet a second time and length of time off-diet were not significantly correlated.

Of the patients who discontinued diet a second time, the median length of time on diet after reinstitution was 10 months. Of patients who remained on diet a second time, the median length of time after diet reinstitution was two years nine months.

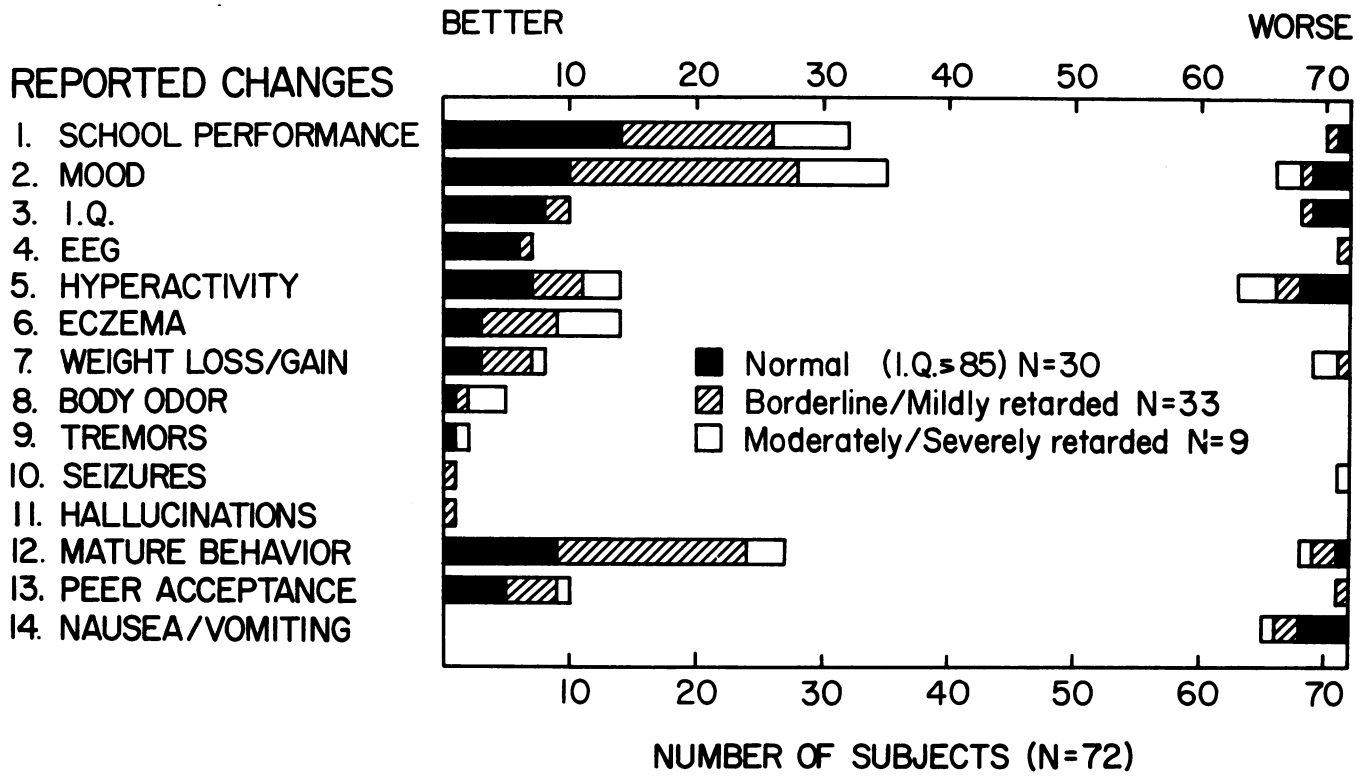

FIGURE 2—Changes in PKU Patients after Diet Reinstitution (empty spaces indicate the number of patients not reported to show change)

There were few patients for whom diet was reinstituted before 1976, and none of these patients remained on diet by the time of the survey. Excluding data from these patients, there was a trend for more females than males to stay on the diet a second time ($r = .210$, $n = 64$, $p < 0.10$). Males were more likely to stay on diet a second time if there were a greater number of improvements in the areas of IQ, school work, mood, and/or EEG ($r = 0.674$, $n = 28$, $p < 0.001$). For females, there was no significant correlation between improvements noted and diet maintenance ($r = 0.265$, $n = 28$, $p > 0.2$), but all except four females remained on diet a second time.

Whether the prime initiator of diet reinstitution was clinic or parents did not make a significant difference in predicting diet maintenance for females. Males were more likely to stay on diet when parents or the patient initiated diet reinstitution rather than the clinic ($r = 0.370$, $n = 33$, $p < 0.05$).

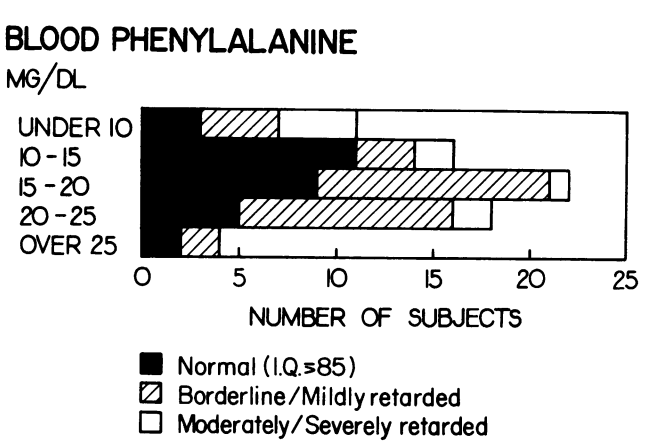

FIGURE 3—Phenylalanine Levels of PKU Patients after Diet Reinstitution (n = 72)

Discussion

This report documents the fact that many clinics in the US now try to reinstitute some form of dietary phenylalanine restriction for patients with PKU who have previously discontinued treatment.

The difficulty of maintaining the PKU diet even when the patient has been on treatment since early infancy is well known. Returning to the diet can be extremely difficult if a patient has developed a liking for high protein foods, and/or has found the PKU formula distasteful. Motivation of both patient and family as well as clinic staff needs to be great. In the authors' experience, even high motivation and support may prove insufficient to result in adequate diet maintenance.

Many of the problems noted during the off-diet period and changes following diet reinstitution are based on subjective impressions. Data are incomplete in some areas.

Few patients in this study who had returned to the diet were able to achieve overall mean blood phenylalanine levels of 10 mg/dl or less which are most commonly considered to constitute optimal dietary control,[6] showing the difficulty of maintaining low blood phenylalanine levels. Our data do not establish that high blood phenylalanine levels are responsible for deterioration off-diet or that lowered blood phenylalanine levels account for improvements after diet reinstitution. In assessing the changes that occurred both off-diet and after diet reinstitution, it is reasonable to assume

that factors other than lowered blood phenylalanine levels may have accounted for at least some of the results (e.g., maturation, growth, and expectations or changes in attitude of persons having contact with those patients). The absence of recorded improvements for any one patient after diet reinstitution may be due to actual lack of change, to incomplete data, to an inadequate time after diet reinstitution, or failure to achieve blood phenylalanine levels low enough to produce change. It is also likely that some of the negative changes noted when patients were off the diet, such as loss of IQ, are irreversible for some individuals. Woolf suggests that IQ changes are a late feature of cerebral insults and may not be observed until after irreversible change has occurred.[10]

Positive changes were reported much more often than negative changes after return to diet. The number of perceived positive changes following diet reinstitution correlated with the length of time the patients had been back on the diet. Since we do not know when positive changes occurred, we cannot assume that the longer time on diet is responsible for the improvements, but the perception of positive changes would tend to reinforce the motivation of parents and/or the patient to maintain diet. Most of those who again discontinued diet did so soon after diet reinstitution. All patients who were severely/profoundly retarded remained on the diet a second time, which may reflect the degree of control which others have over their lives.

While there was no positive correlation between blood phenylalanine levels maintained after diet reinstitution and noted improvements, the possibility of such a relationship cannot be totally excluded. Bickel and Kaiser-Grubel reported greatest improvement in IQ for late-treated patients when blood phenylalanine levels remained in the 1–3 mg/dl range for 74 per cent of the time.[11]

In this study, more females than males remained on the diet a second time. Because diet control during pregnancy offers the hope that women with PKU will bear children undamaged by high intrauterine levels of phenylalanine,[12] females may be more motivated to maintain the diet than males.

Double blind studies of low and high phenylalanine intake can seldom be done with individuals of normal intelligence who live in an unrestricted environment. However, if future studies of diet reinstitution include detailed periodic assessment of various areas in which off-diet problems have been noted, it may be possible to evaluate the effects of reduced plasma phenylalanine levels and the effects of duration of second-time diet maintenance.

We hope that patients with PKU who have discontinued diet will be followed regularly, even decades after discontinuation of diet. Data from patients discontinued from diet can then be compared with data from those patients for whom diet was reinstituted, or with data from those who have been continuously on diet therapy.

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NCRP to Hold 21st Annual Meeting in Washington

The National Council on Radiation Protection and Measurements will hold its 21st annual meeting on April 3–4, 1985 in Washington, DC. The principal scientific session of the two-day conference will focus on "Radioactive Waste." For additional information on the program and registration, contact NCRP, 7910 Woodmont Avenue, Suite 1016, Bethesda, MD 20814. NCRP is a non-government, not-for-profit, congressionally chartered public service organization.