J. Inher. Metab. Dis. 18 (1995) 131–134

Short Communication

Improvements in behaviour and physical manifestations in previously untreated adults with phenylketonuria using a phenylalanine-restricted diet: a national survey

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Untreated adults with phenylketonuria (PKU; McKusick 261600) born prior to newborn screening may have abnormal electroencephalograms, seizures, neurological and behavioural disorders, a distinctive musty odour, eczema, and profound mental retardation. Behavioural aberrations in these individuals include hyperactivity, aggressiveness, negative mood swings, motor and attention disturbances, and self-inflicted injury (Brunner et al 1987; Scriver et al 1989). Behavioural improvement has been reported in previously untreated adults with PKU after introduction of a phenylalanine (PHE)-restricted diet with a subsequent reduction in plasma PHE concentrations (Hambraeus et al 1971; Harper and Reid 1987; Giffin et al 1980; Yannicelli et al 1990; Hoskin et al 1992). Physical manifestations associated with untreated PKU have been ameliorated with proper administration of a PHE-restricted diet and subsequent decline in plasma PHE concentration (Yannicelli et al 1990).

Despite the documented positive behavioural response to a PHE-restricted diet in untreated adults, there have been some concerns. Gilpin et al (1993) reported increased frequency of aggressive behaviour and recurrence of seizure disorders in some individuals after diet initiation. Marholin et al (1978) also reported self-abusive behaviour in one patient given a PHE-restricted diet. Regardless of these few negative case reports, clinicians consider nutrition support a viable therapy for these patients.

Most of the reports on the effectiveness of introducing a PHE-restricted diet have either been individual case studies or have been on small numbers of patients. We attempted to identify the effectiveness of diet intervention in previously untreated adults with a large national survey.

METHODS

A survey was developed to evaluate whether the introduction of a PHE-restricted diet with a concomitant reduction in plasma PHE concentration was associated with

positive physical and behavioural changes and the reduction in the use of psychotropic medications in previously untreated adults with PKU. The survey was mailed to 256 United States public residential facilities for the mentally retarded. Of these, 96 surveys were returned (37.5%). Descriptive statistics were used to calculate frequency responses on 57 usable surveys (22% of the original surveys mailed) that included information on 88 adult patients diagnosed with PKU. The remaining respondents either did not have adults with PKU in their facilities or did not treat these individuals with a PHE-restricted diet. Respondents included dieticians (96%), nurses (2%), and supervisors (2%).

RESULTS AND DISCUSSION

More than half of the reported patients (59%) were started on a PHE-restricted diet after 35 years of age. Reasons for diet initiation varied, but included aberrant and self-abusive behaviour, hyperactivity, poor socialization skills, limited attention span, and physical symptoms (i.e. body odour, eczema). Forty-six per cent of patients had positive behaviour changes after diet intervention. Significant improvements were found in the degree of irritability (66.7%), attention to task (58.8%), hyperactivity (51.4%), aggressive behaviour (46.2%), and incidence of neurological symptoms (25.8%) (Table 1). Our data show that improved behaviour occurred with a reduction in mean concentration of plasma PHE from 1659 μmol/L (range 1000–2330 μmol/L) to 617 μmol/L (range 182–1495 μmol/L). Over half (67%) of the patients attained positive behaviour changes within 3 weeks to 2 months after diet initiation.

Behavioural improvement may be dependent on the availability of plasma and cerebrospinal fluid tyrosine (TYR) for catecholamine synthesis (Lou et al 1987). Few of the survey respondents reported prescribing TYR supplements (22%) for their patients. Approximately half reported monitoring plasma TYR on a frequent basis. Those patients not responding to diet may have failed to adequately reduce plasma PHE, and may also have been TYR deficient (Yannicelli et al 1990; Lou et al 1987).

Degree of mental function may be another reason for lack of behavioural response to diet intervention. Giffin and colleagues (1980) reported that previously untreated patients with PKU displaying higher mental function had greater visual attention span than those patients with lower mental function when provided a PHE-restricted diet.

One respondent in the present study reported that diet was discontinued in a patient secondary to increased self-abusive behaviour. A similar finding was previously reported by Gilpin et al (1993) and Marholin et al (1978). These reports did not state whether the reason for increased aggression was secondary to modification in prescription of antipsychotic/tranquillizer drugs or changes in behaviour modification programmes. Theoretically, a reduction in plasma PHE concentration and a concomitant increase in brain TYR concentration may increase catecholamine synthesis (Gibson and Wurtman 1978), which acts as a stimulant, thereby increasing irritability.

A reduction in the use of psychotropic drugs was reported in 40% of patients who showed behavioural improvement. Chronic administration of antipsychotic/tranquillizer medications has been associated with various medical complications including anaemia and peripheral oedema. For this reason, diet intervention would be the therapy of choice.

Table 1 Percentage of previously untreated adults with PKU showing improvement in physical, behavioural, and neurological manifestations after initiation of a PHE-restricted diet

Symptoms	*Percentage of patients showing improvement*
Physical	
Weight gain	38.0
Weight loss	23.0
Hair loss	2.0
Eczema	38.0
Improved body odour	30.0
Improved appetite	32.0
Behavioural/neurological	
Hyperactivity	51.0
Mood swings	46.2
Irritability	66.7
Attention to task	58.8
Aggressiveness	46.2
Activities of daily living	34.0
Seizures	11.0
Gross neurological	25.8

Patients were noted to have positive changes in weight (38%), and amelioration of eczema (38%) and body odour (30%) (Table 1). The relationship between hyperphenylalaninaemia and eczema has not been elucidated, but may be due to TYR deficiency (Francois et al 1989). Skin creams are often prescribed for untreated adults with PKU and eczema, but without much improvement. A reduction in plasma PHE concentration through diet intervention may be the only available means for treating this skin disorder.

The success of the PHE-restricted diet in treating these patients may be dependent on the proper management of psychotropic medication and behaviour modification programmes. Snyder et al (1993) reported increased disruptive behaviour in one patient when psychotropic medication was reduced; 'behavioural programming' changes were initiated simultaneously. Eighty per cent of the facilities who responded to this survey used behaviour modification programmes in conjunction with a PHE-restricted diet.

The results from this survey support the premise that for approximately half of previously untreated adults with PKU a PHE-restricted diet and subsequent reduction in plasma PHE concentration can improve aberrant behaviour and PKU-related symptoms, and reduce the use of psychotropic medications. Nutrition support for these patients should be considered a viable option for treatment.

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