Ann. Ist. Super. Sanità, vol. 31, n. 4 (1995), pp. 489-502

Nutrition in children affected by inherited metabolic diseases

Marcello GIOVANNINI, Giacomo BIASUCCI, Diego LUOTTI, Laura FIORI and Enrica RIVA

Clinica Pediatrica, Ospedale San Paolo, Università degli Studi, Milan, Italy

Summary. - Diet-therapy represents an elective approach to the treatment of several inborn errors of metabolism. According to the type of disease, dietary intervention can be addressed to three different goals: a) dietary restriction (global or partial) of one or more nutritional components become "toxic" because of the occurring enzymatic defect; b) supplementation with a given defective nutritional component; c) elimination through the use of diet and drugs of the accumulated "toxic" compounds. These interventions are aimed at overtaking the metabolic block and to avoid the accumulation of intermediate "toxic" substrates. The efficacy of the therapy should then be evaluated by means of a thorough biochemical and clinical follow-up (including anthropometric and psychomotor development parameters). In particular, nutritional indexes should be constantly monitored in order to support the dietary therapy, discover and correct any possible nutritional deficiency secondary to the "by exclusion dietary regimen". To elucidate these general principles, we discuss in detail some hereditary diseases of amino acid (phenylketonuria) and carbohydrate (glycogen storage disease and galactosemia) metabolism that, being responsive to the nutritional intervention, can be considered reliable examples of all the problems linked to diagnosis, acute and long-term therapy and follow-up of these diseases.

Key words: diet-therapy, phenylketonuria, glycogen storage disease, galactosemia.

Riassunto *(L'alimentazione nei bambini affetti da patologie metaboliche congenite)*. - La dieta rappresenta l'approccio elettivo alla terapia clinica di numerose malattie metaboliche congenite. In base all'entità nosologica da trattare, l'intervento dietetico si può esplicare secondo tre differenti modalità: a) restrizione dietetica globale o parziale di una o più componente nutrizionale divenuta "tossica" a causa del blocco enzimatico presente; b) supplementazione di una singola componente nutrizionale primitivamente o secondariamente deficitaria; c) eliminazione mediante supporto dietetico e farmacologico dei substrati "tossici" accumulati. Questi interventi hanno lo scopo di superare l'ostacolo metabolico o di evitare l'accumulo di intermedi ad azione potenzialmente tossica. La validità dell'intervento terapeutico viene quindi valutata mediante il monitoraggio costante dell'equilibrio metabolico ed il controllo clinico dei parametri auxometrici e dello sviluppo psicomotorio. In particolare, gli indici nutrizionali devono essere a loro volta attentamente e costantemente monitorati per non invalidare la terapia intrapresa e poter correggere prontamente eventuali squilibri e/o deficit secondari. Tali indagini consentono inoltre il controllo delle conseguenze metabolico- nutrizionali legate al particolare pattern alimentare. Allo scopo di esemplicare quanto affermato, vengono discusse in dettaglio alcune patologie congenite del metabolismo aminoacidico (fenilchetonuria) e glicidico (glicogenosi e galattosemia), che, rispondendo positivamente all'intervento nutrizionale, si possono considerare a ragione esempi paradigmatici delle problematiche che la gestione di tali patologie comporta in termini di diagnosi, terapia in fase acuta e a lungo termine e follow-up clinico-metabolico.

Parole chiave: dietoterapia, fenilchetonuria, glicogenosi, galattosemia.

Introduction

In 1909, when Sir Archibald Garrod first described four "inborn errors of metabolism" as blocks in the normal flow of metabolic processes, arose the concept that genes control metabolism and that inherited metabolic diseases are caused by those metabolic blocks, yelding accumulated precursors and deficient products.

Today, over 3000 monogenic human disorders are catalogued, about 400 of which have a defined biochemical basis. Of these, over 200 genetic disorders lead to harmful manifestations related to toxicity, deficiency or overproduction of normally occurring substrates and products of metabolic flow.

While we wait for a new basic solution to "hereditary metabolic diseases" that the growing amount of studies on enzyme and gene therapy might hopefully provide in the near future, the current therapeutic approach to these diseases is still based on modification of the dietary supply.

The so called "dietary therapy", when started before an irreversible damage has occurred, helps preventing the affected children by an altered growth and differentiation of the different tissues and nervous system, or at least reduces the damage severity by modulating its pathophysiogenetic mechanisms.

Depending on the different pathophysiology of disease expression, several therapeutic strategies could be used, sometimes simultaneously [1]:

a) dietary restricition of accumulated toxic substrate(s), either by means of global modification (protein, carbohydrate and lipid fraction) or by excluding selected nutritional components (i.e. galactose or fructose).

Examples are phenylketonuria (PKU), maple syrup urine disease (MSUD), urea cycle disorders (UCD) for which limited intake of phenylalanine (phe), brached chain amino acids (leucine, isoleucine and valine) or whole proteic fraction is mandatory, and galactosemia, in which only galactose-containing foods are restricted.

b) Replacement and supplementation of deficient components (vitamins as cofactors, single amino acids, carnitine). Vitamin dependent diseases as homocystinuria (vit. B_6), MSUD (vit. B_1), methylmalonic acidemia (vit. B_{12}) or propionic acidemia (biotin), as well as those hereditary diseases involving carnitine metabolism, may dramatically benefit from a pharmacological intake of these specific compounds.

c) Limitation of toxic compound accumulation and enhancement of overproduced toxic substance excretion. An example of this can be supplying benzoic acid in hyperammoniemia, thus providing an alternate metabolic pathway to limit ammonia accumulation and to enhance its urinary excretion, or giving allopurinol in gout or glycogen storage disease (GSD) type I, thus lowering uric acid production.

The clinical and biochemical follow-up schedule that these patients should strictly follow enables the physicians to record very promptly any metabolic and nutritional consequence of such a dietary regimen, justifying the definition of *experimenta naturae* attributed to hereditary metabolic diseases.

Some paradigmatic diseases, concerning amino acid and carbohydrate metabolism, will be discussed.

Phenylketonuria

The reason why phenylketonuria (PKU) [2] will be discussed in detail is that its dietary treatment and nutritional approach can be used as a model for many other disorders of amino acid metabolism.

PKU includes a group of hereditary disorders of phenylalanine metabolism caused by impaired phenylalanine hydroxylase activity. The disease is clinically expressed at three to six months of age and is characterized by severe and progressive developmental delay, hyperactivity, irritability, microcephaly, abnormal electroencephalogram and eczema. The pathogenetic mechanisms of the neurological damage are still not fully understood, although the following hypotheses [3-6] seem to be the most widely accepted: a) altered myelin proteo-lipid metabolism and accelerated myelin turn-over directly caused by high phe plasma levels; b) depressed protein synthesis in the brain due to competitive mechanisms between phe and other large neutral amino acids for the passage through the blood-brain barrier; c) reduced neurotrasmitter synthesis for the inhibitory effects of high phe in the brain on tyrosine and tryptophan hydroxylases.

Biochemically, it becomes evident as soon as the infant starts feeding, with plasma phe levels constantly above 2 mg/dl. Three different variants, according to the severity of the enzymatic loss are so far known, with a global incidence in Italy of about 1:10000 newborns: a) classical PKU (hyperphenylalaninemia-HPA, type I) with pre-treatment phe plasma levels above 20 mg/dl and the most severe clinical manifestations due to the almost nil enzymatic activity; b) mild PKU (HPA II), in which the residual enzymatic activity is able to maintain pre-treatment phe plasma levels between 10 and 20 mg/dl; no mandatory psychomotor retardation; c) non-PKU HPA (HPA III) with a fairly high residual activity, which is enough to keep phe plasma levels constantly below 10 mg/dl on a free diet and development within normal range.

Other forms of HPA derive from a defect in the cofactor tetrahydrobiopterin (BH4) metabolism, affecting either its synthesis or regeneration from the non-functional state.

At present four forms of BH4 deficient HPAs [7] are known, globally accounting for about 1-3% of all HPAs. They are clinically expressed within the first trimester of life with severe neurological impairment (muscle hypotone of the trunk, hypertone of the limbs, myoclonic seizures, difficulties in swallowing) up to lethargy, coma and early death. The severity of clinical manifestations is caused by a lacking synthesis of neurotransmitters as dopamine and serotonin, in turn caused by the lack of BH4 activity. BH4, in fact, acts as a cofactor not only for phe, but also for tyrosine and tryptophan hydroxylases, which synthesize L-dopa and 5-OH tryptophan, the direct precursors of the mentioned neurotransmitters.

This explains why BH4 deficiencies require supplementation with L-dopa, 5-OH-tryptophan and synthetic BH4, besides dietary treatment similar to that for classical PKU.

If not diagnosed and treated within the first three to six weeks of life, classical PKU leads to severe and irreversible psychomotor retardation, due to the permanent damaging mechanism on myelin turn-over by high phe plasma concentrations.

It is therefore common agreement to start treating newborn babies being positive at neonatal screening for PKU (Guthrie test at 4th day of life) as soon as their hyperphenylalaninemia has been confirmed by means of ion exchange liquid chromatography (on average within three weeks of life) when their phe plasma levels keep constantly above 6 mg/dl.

So far the only effective therapy for PKU is still represented by an appropriate diet, which is aimed at preventing toxic effects of high plasma phe on the

nervous system, while providing an adequate intake of essential amino acids for growth.

Diet is constituted by very few animal proteins (the richest in phe) which are usually provided either by human milk or by the poorest in the phe milk formula available, mainly vegetable foods and fruit (after weaning) and caloric supplements to meet lipid and carbohydrate requirements (mainly vegetable oils and maltodextrin mixtures), resulting in a very characteristic nutritional pattern (Table 1).

To meet daily protein requirements for growth, specific and dedicated phe free amino acid mixtures are added to the diet (Tables 2, 2a, 2b) [8].

The common therapeutic approach to the PKU child is to promply start a phe free diet (Table 3), in order to obtain a rapid decline of plasma phe concentration within the treatment range.

Plasma phe drops to normal level usually in 3-4 days, but the time required may vary up to one week, depending on the pre-treatment level.

Once plasma phe has dropped to normal range (2-6 mg/dl throughout school age), phe (essential amino acid) should be re-introduced in the diet, at a starting dose of 20 mg/kg/day (Table 4), constantly monitoring plasma phe levels (twice a week). In case the patient has an higher dietary phe tolerance, as for HPA II children, dietary phe intake may be progressively increased up to 40 mg/kg/day and even more.

In order to ensure variety of the dietary pattern and make it more acceptable to the affected children, we utilize the "ponderal equivalent method" [9], specific for substituting cereals and milk or vegetables and fruit. Parents are given two lists of natural and manufactured products showing the amount of each product corresponding to "one equivalent" of phe, which we decided to be 10 mg for cereals and milk products and 20 mg for vegetables and fruit. Following this method, parents are free to choose different foods, according to the personal preference of their children, without changing the total amount of phe daily intake.

Dietary regimen is then frequently adjusted, according to growth (every 500 g weight gain) and to plasma phe levels, which should be checked twice a week for the first 3 months, weekly up to 12 months and then fortnightly (Table 5) [10].

Requirements for protein, carbohydrate and lipid intake, are met according to LARN statements [11].

On the basis of studies demonstrating that myelin turnover seems to work also in adulthood, it is now widely agreed that diet should be prolonged for the whole life.

Due to diet peculiarity ("by exclusion" diet, providing nearly nil intake of animal proteins), PKU children may become at risk for important nutritional deficiencies, adding new potential damage to the biochemical one already there.

In particular the risk concerns those dietary factors found especially in products of animal origin. These components are known as "conditioned essentiality": they are present and can be synthesized only minimally in animals, but most of them come from exogenous intake.

Trace elements, taurine, carnitine and lipid/cholesterol and very long chain polyunsatured (VLCP) fatty acids are currently the molecules most investigated for this.

Based on previous findings of reduced plasma concentration of iron, ferritin, zinc, copper and selenium in treated PKU children [12], current formulas and amino acid mixtures have been supplemented in order to help prevent any secondary deficiency of these compounds. Normal manganese plasma level is guaranteed by the high manganese content of vegetables, while selenium is still reported to be low. It is currently under study the ideal mode of supplementation of this important anti-oxidant.

Althought no clinical symptom of taurine and carnitine deficiency has been so far reported, several studies demonstrated that treated PKU children display low plasma levels of these two compounds [13, 14].

Since taurine plays an important functional role in stabilizing the nerve membranes of the retina and of the central nervous system and in regulating the signals between nerve cells, and since carnitine is a fundamental carrier for mitochondrial beta-oxidation of fatty acids, it is advisable that they are supplemented in the formulas utilized in PKU children's diet.

Even though the PKU diet offers an "eulipid" model, with almost nil cholesterol intake and favorable intralipid rations (high intake of unsaturated and low intake of saturated fats) [15], it results deficient as regards the supply of VLCP fatty acids.

VLCP fatty acids are found preformed mainly in animal products, so that the low dietary intake of PKU children explains their relative deficiency [16]. The most

Table 1. - Mean daily nutrient intake in treated hyperphe children *vs* healthy controls

Nutrient	Hyperphe	Controls
kcal/kg/day	71 ± 10	78 ± 28
Protein (%)	8.6 ± 1.6	15 ± 1.2
Carbohydrate (%)	67.1 ± 8.0	49.3 ± 0.8
FAT (%)	24.3 ± 7.9	35.4 ± 0.6
Oleic acid (%)	12 ± 1.1	14 ± 1.3
Linoleic acid (%)	6.6 ± 1.9	3.9 ± 0.9
Cholesterol (mg/1000 kcal)	10 ± 3.0	153 ± 14
P/S ratio	1.1	0.3
M/S ratio	1.8	0.9

P: polyunsaturated fatty acids.
M: monounsaturated fatty acids.
S: saturated fatty acids.

Table 2. - Hyperphenylalaninemia: composition of dietary products available in Italy

Per 100 g of product	PKU 1 *(a)*	PKU 2 *(b)*	MAXA MAID 1*(a)*	MAXA MAID 2*(b)*	MAXA MAID 3*(c)*	Phenyl free *(d)*	Phenyl don *(d)*	Lofena lac *(d)*	MAXA MUM *(e)*	PKU 3 *(e)*
Protein (g)	50	67	15.5	77.8	25	20	53.4	15	41	68
Amino acids (g)	60	80	18.6	93.2	30	24	66.7	18	49	81
Carbohydrates (g)	19	7	54	4	61	66	16.5	60	41.3	3
Source	sucrose	sucrose	galactose maltodextrins	maltodextrins	sucrose maltodextrins	sucrose corn syrup solids, modified tapioca starch	glucose maltose polysaccharides	corn syrup solids, modified tapioca starch	sucrose, maltodextrins	sucrose
Fat (g)	0	0	23	0	< 0.5	6.8	0	18	0.5	0
Vitamins & minerals (g)	17.6	9.7	1.7	0	4	2.3	11.5	1.9	7.3	12.4
Water (g)	2	2	6	2.7	< 4.5	3.2	0	3.8	2.4	2
Calories (cal)	280	300	485	326	349	410	319	460	329	290

(a): for infants from 0 to 12 months of age
(b): for children from 12 to 24 months of age
(c): for children above 24 months of age
(d): for infants, children and adults
(e): for pregnant PKU women

Table 2a. - Hyperphenylalaninemia: nutrients of dietary products available in Italy. Nutrient level of the added vitamins and minerals in 100 g of each product

	PKU 1	PKU 2	MAXA MAID 1	MAXA MAID 2	MAXA MAID 3	Phenyl free	Phenyl don	Lofena lac	MAXA MUM	PKU 3
Vitamin A (IU)	9300	5200	1549	0	872	1220	5100	1430	2090	4000
Vitamin D (IU)	1000	1310	300	0	400	152	450	290	400	480
Vitamin E (IU)	34	18	4.9	0	5.9	10.2	23	14.3	7.1	12
Vitamin K (mcg)	167	167	45	0	30	102	0	72	20	167
Vitamin B_1 (mcg)	2700	1400	400	0	1200	610	0	360	500	1800
Vitamin B_2 (mcg)	4000	2000	600	0	1200	1020	0	430	1400	1800
Vitamin B_6 (mcg)	2200	1500	0	0	0	910	2100	290	2100	3200
Vitamin B_{12} (mcg)	7.9	3	1.0	0	3.9	2.5	4.5	1.43	4	5
Niacin (mcg)	54000	24000	4500	0	12000	8100	23000	5800	0	1800
Folacin (mcg)	340	400	38.5	0	150	127	570	72	500	950
Pantothenic acid (mcg)	25000	11000	2650	0	3700	3000	11000	2200	3100	8300
Biotin (mcg)	100	300	26	0	120	30	340	36	140	179
Vitamin C (mg)	230	80	41	0	135	53	125	37	80	100
Choline (mg)	430	260	65	0	270	86	530	61	320	260
Inositol (mg)	500	300	100	0	55.5	30	510	22	85.7	300
Ca (mg)	2400	1310	325	0	950	510	1070	430	640	1310
P (mg)	1860	1010	860	0	3100	510	800	320	800	1010
Mg (mg)	520	156	36.6	0	223	152	225	50	285	540
Fe (mg)	34	15	10.1	0	14.3	12.2	23	8.6	24	21
Zn (mg)	26	78	4.3	0	19.5	7.1	16	3.6	14	24
Mn (mcg)	2400	700	600	0	1400	1020	9300	143	3000	4800
Cu (mcg)	6700	2000	300	0	1860	610	2600	430	1600	3600
I (mcg)	230	120	0	0	100	46	130	32	100	143
Na (mg)	1070	640	160	0	570	410	1070	220	600	640
K (mg)	2300	1330	430	0	870	1370	3200	470	700	1330
Cl (mg)	1650	990	300	0	700	930	1930	320	560	1000

Table 2b. - Hyperphenylalaninemia: amino acids of dietary products available in Italy (g/100 g powder)

Per 100 g	PKU 1	PKU 2	MAXA MAID 1	MAXA MAID 2	MAXA MAID 3	Phenyl free	Phenyl don	Lofena lac	MAXA MUM	PKU 3
His	1.4	1.8	0.63	3.7	1.35	0.46	1.8	0.49	1.8	1.8
Ile	3.4	4.5	0.94	5.67	1.74	1.08	3.8	0.87	2.8	4.5
Leu	5.7	7.6	1.61	10.01	3.01	1.7	6.1	1.7	4.8	7.6
Lys	4.0	5.4	1.27	7.7	2.35	1.86	4.3	1.66	3.67	5.4
Met	1.4	1.8	0.23	1.57	0.51	0.62	1.8	0.55	0.77	1.8
Cys	1.4	1.8	0.41	2.36	0.76	0.34	1.5	0.06	1.17	1.8
Phe	0	0	0	0	0	0	0.02	0.075	0	0
Tyr	3.4	6.0	1.42	8.6	2.71	0.93	6.7	0.80	4.24	6.0
Thr	2.7	3.6	0.83	4.97	1.51	0.93	3.2	0.79	2.35	3.6
Trp	1.0	1.4	0.31	1.93	0.61	0.28	1.5	0.20	0.94	1.4
Val	4.0	5.4	1.02	6.14	1.96	1.240	4.0	1.38	3.07	5.4
Ala	2.4	3.1	0.59	3.62	1.09	0	2.6	0.68	1.68	3.1
Asp	5.7	7.6	1.11	6.19	1.96	5.2	5.8	1.40	2.96	7.6
Glu	12.0	16.0	1.65	10.2	2.51	6.6	10.7	4.00	4.8	16.0
Gly	1.4	1.8	1.09	6.36	1.85	3.3	1.5	0.38	2.97	1.8
Pro	5.4	7.1	1.16	7.14	2.15	0	5.5	1.42	3.4	7.1
Ser	3.0	4.0	0.71	4.34	1.32	0	3.6	0.94	2.1	4.0
Arg	2.0	2.7	1.1	6.68	2.35	0.68	2.3	0.56	3.18	2.7

deficient very long chain N-3 and N-6 derivatives are eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids and arachidonic acid (AA).

EPA and especially DHA are known to be "growth factors" for the central nervous system, in particular for the retina and the optic ways in the first months of life, being fundamental structural components of cell membranes [17].

Substances derived from AA mediate immunoallergic responses, regulate cardiovascular parameters and are important for the development of the nerve cell membranes. Dietary deficiency of AA, the consequent limited synthesis of its proinflammatory mediators, together with the low antigen load from complete animal proteins, could explain some findings in treated PKU children who showed an overall reduction of allergic symptoms compared to controls, despite higher plasma levels of IgE and a lower humoral immune stimulation reflected in lower IgG, IgA and IgM at all pediatric ages [18].

On-going studies will assess whether PKU children could derive some clinical and biochemical benefit from a dietary supplementation with VLCP fatty acids.

The risk for the mentioned nutritional deficiencies secondary to the peculiar dietary pattern increases in conditions of enhanced demand, such as in the case of "maternal PKU".

Table 3. - Example of phenylalanine free diet for HPA children (age: 15 days; weight: 3700 g)

Food	Quantity (g)
MAXA MAID 1	48
Olive oil	13
Maltodextrins	20

All mixed in water (at least 640 ml) to be divided in 7 bottles

Food	Quantity (g)	Phe (mg)	Protein (g)	Carbohydrate (g)	Lipid (g)	Calories
MAXA MAID 1	48	0	8.06	26.88	11.28	235.20
Olive oil	13	0	0	0	13	117.00
Maltodextrins	20	0	0.06	18.84	0	76.00
Total	81	0	8.12	45.72	24.28	428.20
Protein % = 7.59	Carbohydrate % = 40.04		Lipid = 51.03			

Protein intake: 2.20 g/kg/day.
Calorie intake: 115.73 kg/day.

Table 4. - Example of diet providing phenylalanine 20 mg/kg/day for HPA children (age: 15 days; weight: 3700 g)

Food	Quantity (g)
MAXA MAID 1	40
Olive oil	9
Maltodextrins	12
Human milk	150

All (but human milk) mixed in water (at least 485 ml) to be divided in 5-6 bottles

Food	Quantity (g)	Phe (mg)	Protein (g)	Carbohydrate (g)	Lipid (g)	Calories
MAXA MAID 1	40	0	6.80	22.68	9.52	198.45
Olive oil	9	0	0	0	9	81.00
Maltodextrins	12	0	0.04	11.30	0	45.60
Human milk	150	72	1.34	10.50	5.55	103.50
Total	211	72	8.18	44.48	24.07	428.55
Protein % = 7.63	Carbohydrate % = 39.93		Lipid % = 50.54			

Protein intake: 2.21 g/kg/day.
Calorie intake: 115.82 kg/day.

Table 5. - Follow-up protocol of treated HPA children during the first two years of life

	Age (months)												
	Diagnosis	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Clinical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Anthropom. parameters	X			X			X			X			X
Bone age				X			X						X
Nutritional parameters	X			X			X						X
Neurophysiol. parameters	X						X						X
Neuropsychol. parameters										X			X
Ophtalmol. examination	X						X						X
Plasma phe (Guthrie test)	Twice a week				Once a week					Fortnightly			

This term defines a new field of interest for physicians who deal with PKU, represented by the pregnacies of treated PKU women.

High phe plasma levels are responsible for the severe embriofetopathy (microcephaly, heart defects, etc.) affecting the offsprings of untreated PKU mothers.

Studies have defined 6 mg/dl plasma phe as the threshold level for toxic effects to occur in the fetus.

It is therefore fundamental to thoroughly monitor PKU women throughout pregnancy, ensuring plasma phe normalization before conception and then maintaining the therapeutic range by means of an appropriate dietary regimen.

Due to the augmented request of the growing fetal tissues, pregnancy is the extreme situation in which a deficiency in nutrients of "conditioned essentiality" is most likely to occur.

In particular, VLCP fatty acids have been found to be low in treated PKU pregnant women; proper supplementation with N-6 and N-3 very long chain derivatives are effective in restoring normal levels [19].

In conclusion, the follow-up of HPA children, as well as of those children affected by other metabolic disorders whose therapy is based on a life-long dietary treatment demands a great commitment from physicians. The original "dietary therapy" in fact is gradually becoming "nutritional therapy", which is not confined to the elaboration of low-phe regimens, but contributes to a better prognosis for the affected children by applying the latest knowledge on the biochemistry and physiology of nutrition.

Other inborn errors of amino acid metabolism

The general principles expressed for dietary therapy of PKU are also valid for the other disorders of amino acid metabolism requiring a long-term diet as tyrosinemia, urea cycle disorders, organic acidemias and maple syrup urine disease [20].

Protein intake should be restricted once the enzymatic defect has been assessed, with the aim of preventing accumulation of a given amino acid and/or metabolite and their toxic effects on the different organs.

The allowed protein intake, necessary for growth, should better be guaranteed by supplying proteins of high biological value as it is for human milk or an infant milk formula. After weaning a variety of foods, including low-protein cereals, vegetables and fruit, is introduced. An exchange system of foods with the amino acid or protein content equivalent to one "unit" is useful and allows variety (as it is for the "ponderal equivalent method" in PKU).

To meet the daily protein requirements, without providing the given "toxic" amino acid(s) (phe or tyrosine, methionine, leucine, isoleucine, valine, threonine, according to the different diseases), a number of protein substitutes are available on the market for the specific inborn error of amino acid metabolism (Tables 6, 6a).

They usually are synthetic amino acid mixtures, free of the "toxic" amino acid(s); they are not a complete diet and all of them require supplements of essential fatty acids, vitamins and minerals.

The protein substitutes are often unpalatable and sometimes bitter; for this reason, and for nutritional interactions, they should not be administered alone, but mixed with milk or other food.

Similar to the protocol for low-phe diets, vegetables and fruit are permitted in large but controlled quantities, owning to their lower protein intake.

Once protein intake has been assessed for the specific metabolic disorder in order both to maintain a good metabolic balance and a sufficient intake for growth, the diet should be adjusted for the energy requirements for sex and age.

As for PKU, this is done by adding carbohydrate sources and vegetable oils, which are also useful to ensure a favourable lipidemic pattern and to prevent secondary nutritional deficiencies of essential fatty acids.

With regard to minerals and vitamins, although most of them are currently added to infant formulas and amino acid mixtures and are present in vegetables and fruit, it is advisable to supplement diets as for PKU. In particular, some vitamins, as vitamin B_{12}, C, biotin and thiamine may also play a key therapeutic role, besides diet, in specific diseases as respectively methylmalonic acidemia, neonatal transient tyrosinemia, propionic acidemia and maple syrup urine disease. Acting as cofactor of specific enzymes, pharmacological doses may restore normal enzymatic activity.

Feeding problems are relatively common in children undergoing long-term restricted diets, and are particularly common in children with the classical forms of organic acidemias and urea cycle disorders, as the toxic metabolite(s) causes anorexia.

Parental support and advice is extremely useful and it should be given as early as this problem arises. If nutritional problems, poor growth and poor metabolic control occur, long-term enteral nutrition with appropriate food should be considered.

Unlike PKU, the emergency treatment required during metabolic stress in many disorders of amino acid metabolism is quite distinct from their long-term management.

Infection, illness, starvation, vomiting and/or diarrhoea increase endogenous protein catabolism with the release of large quantities of "toxic" amino acids and/or metabolites which lead to acute biochemical and clinical deterioration.

This may be accompanied by metabolic acidosis, hypoglycaemia, hyperammonaemia, that are potentially life-threatening.

Table 6. - Histidinaemia, homocystinuria, lysinuria. Dietary products available in Italy: composition-amino acids (g/100 g powder)

Per 100 g	HIST 1 *(a)*	HIST 2 *(b)*	ASTIDIN	HISTI DON	HOM 1 *(a)*	HOM 2 *(b)*	AMETIO NIN	LYS 1 *(a)*	LYS 2 *(b)*
Protein (g)	51	67	82	81	52	69	81	48	64
amino acid (g)	61	81	99	97.3	62	82	97	58	77
Carbohydrate (g)	17	7	0	0	18	5	0	23	12
Source	sucrose	sucrose	-	-	sucrose	sucrose	-	sucrose	sucrose
Fat (g)	0	0	0	0	0	0	0	0	0
Vitamin & mineral (g)	16.9	9.7	0	0	17.6	9.7	0	17.6	9.7
Water (g)	2	2	-	-	2	2	-	2	2
Calories (cal)	270	300	330	-	280	300	323	280	300
His	0	0	0	0	1.4	1.8	4.3	1.4	1.8
Ile	3.4	4.5	6.25	9.3	3.4	4.5	5.89	3.4	4.5
Leu	5.7	7.6	10.69	9.3	5.7	7.6	10.26	5.7	7.6
Lys	4.0	5.4	9.01	6.6	4.0	5.4	8.66	0	0
Met	1.4	1.8	1.71	2.7	0	0	0	1.4	1.8
Cys	1.4	1.8	2.54	2.3	2.5	3.4	2.38	1.4	1.8
Phe	2.4	3.2	4.66	3.7	2.0	3.2	4.44	2.4	3.2
Tyr	2.9	3.9	3.55	4.9	2.9	3.9	3.38	2.9	3.9
Thr	2.7	3.6	5.24	4.9	2.7	3.6	4.97	2.7	3.6
Trp	1.0	1.4	2.74	2.2	1.0	1.4	2.56	1.0	1.4
Val	4.0	5.4	7.13	6.1	4.0	5.4	6.96	4.0	5.4
Ala	2.4	3.1	3.79	4.0	2.4	3.1	3.52	2.4	3.1
Asp	5.7	7.6	6.68	8.8	5.7	7.6	6.63	5.7	7.6
Glu	12.0	16.0	7.92	16.3	12.0	16.0	7.51	12.0	16.0
Gly	1.4	1.8	6.61	2.3	1.4	1.8	6.08	1.4	1.8
Pro	5.4	7.1	7.66	8.3	5.4	7.1	7.27	5.4	7.1
Ser	3.0	4.0	4.71	5.5	3.0	4.0	4.39	3.0	4.0
Arg	2.0	2.7	8.11	3.6	2.0	2.7	4.39	2.0	2.7

(a) for infants from 0 to 12 months of age.
(b) for children above 12 months of age.

Table 6a. - Tyrosinemia, MSUD, organic acidemias, urea cycle disorders. Dietary products available in Italy: composition-amino acids (g/100 g powder)

Per 100 g	TYR 1 *(a)*	TYR 2 *(b)*	ATIRO SIN	TYRO SIDON	MSUD 1 *(a)*	MSUD 2 *(b)*	AVA LIN	LEUCI DON	OS 1 *(a)*	OS 2 *(b)*	UCD 1 *(a)*	UCD 2 *(b)*
Protein (g)	47	63	80.3	81	41	54	81.2	80.3	42	56	56	67
amino acid (g)	57	76	97	97.2	49	65	97.5	97	51	67	68	81
Carbohydrate (g)	21	12	0	0	29	22	0	0	29	20	8	6
Source	sucrose	sucrose	-	-	sucrose	sucrose	-	-	sucrose	sucrose	sucrose	sucrose
Fat (g)	0	0	0	0	0	0	0	0	0	0	0	0
Vitamin & mineral (g)	17.6	9.7	0	0	17.6	9.7	0	0	17.6	9.7	20.2	9.7
Water (g)	2	2	3	-	2	2	2.5	-	2	2	2	2
Calories (cal)	270	300	323	-	280	310	325	-	280	300	260	290
His	1.4	1.8	4.38	3.1	1.4	1.8	5.54	3.4	1.4	1.8	3.1	3.6
Ile	3.4	4.5	6.31	6.6	0	0	0	0	0	0	7.6	8.9
Leu	5.7	7.6	10.91	10.1	0	0	0	0	5.7	7.6	12.8	15.0
Lys	4.0	5.4	9.21	7.2	4.0	5.4	11.20	8.2	4.0	5.4	9.0	10.7
Met	1.4	1.8	1.6	0	1.4	1.8	1.95	3.3	0	0	3.1	7.1
Cys	1.4	1.8	2.58	2.5	1.4	1.8	3.14	2.8	1.4	1.8	3.1	0
Phe	0	0	0	0	2.4	3.2	5.68	4.6	2.4	3.3	5.3	14.1
Tyr	0	0	0	0	2.9	3.9	4.39	6.0	2.9	3.9	6.5	0
Thr	2.7	3.6	5.33	5.4	2.7	3.6	6.39	6.0	0	0	6.0	7.1
Trp	1.0	1.4	2.71	2.4	1.0	1.4	3.29	2.7	1.0	1.4	2.2	2.8
Val	4.0	5.4	7.52	4.0	0	0	0	0	0	0	9.0	10.7
Ala	2.4	3.1	3.8	4.4	2.4	3.1	4.49	4.9	2.4	3.1	0	0
Asp	5.7	7.6	6.92	9.6	5.7	7.6	8.31	10.9	5.7	7.6	0	0
Glu	12.0	16.0	8.27	17.8	12.0	16.0	9.71	19.9	12.0	16.0	0	0
Gly	1.4	1.8	6.74	2.5	1.4	1.8	8.19	2.8	1.4	1.8	0	0
Pro	5.4	7.1	7.79	9.2	5.4	7.1	9.57	10.2	5.4	7.1	0	0
Ser	3.0	4.0	4.79	6.0	3.0	4.0	5.69	6.8	3.0	4.0	0	0
Arg	2.0	2.7	8.14	4.0	2.0	2.7	9.96	4.5	2.0	2.7	0	0

(a) for infants from 0 to 12 months of age
(b) for children above 12 months of age.

The acute illness should be treated rigorously. Temporary omission of protein intake, together with appropriate energy intake, by providing concentrated carbohydrate i.v. solutions is recommended, together with a proper correction of hypoglycaemia and metabolic acidosis. When hyperammonaemia occurs, oral or i.v. supplement with sodium benzoate, arginine or citrulline (according to the enzymatic block in urea cycle) helps prevent acute neurological damage.

Hospitalization is commonly required, particularly when vomiting persists.

Once clinical and biochemical picture is restored to normal, the regular dietary protocol, including proteins, should be progressively re-introduced.

Since dietary treatment of amino acid disorders is highly complex and the life-long dietary management requires a thorough biochemical, clinical and neurophysiological follow-up, these children should be treated in centers with appropriate expertise, including biochemical, nutritional and psychological facilities.

Inborn errors of carbohydrate metabolism

Glycogen storage disease (GSD) type I

Glycogen consists of glucose molecules linked together into a branched chain and it is the body's major carbohydrate reserve.

It is synthesized in the liver from glucose, whose plasma omeostasis is maintained by its release from the liver, and is dependent on adequate glucose-6 phosphatase activity whether the glucose-6 phosphate is derived from glycogen degradation or synthetized from galactose, fructose, glycerol or amino acids [21].

In GSD type I, which is the most common among glycogen storage diseases, there is a deficiency of glucose-6 phosphatase, resulting in severe hypoglycaemia, unless blood glucose is maintained by a regular intake of dietary glucose polymers.

The severe hypoglycaemic and ketoacidotic episodes occurring in GSD type I can permanently damage the central nervous system, being associated with pallor, sweating, weakness, nausea, vomiting, mental confusion, convulsions and coma.

On the long-term, growth retardation, hyperlipidaemia and hypeuricaemia occur; an appropriate management is usually able to overcome these effects secondary to recurrent hypoglycaemic episodes.

The treatment of GSD type I is still based on appropriate diet, which is aimed to maintain blood glucose within normal range throughout the 24 hours by providing regular carbohydrate administration subdivided in frequent meals.

During the first two years of life, this is done by providing meals every three hours, adjusting the global calorie intake according to the calorie requirement for age and sex; diet should provide at least 65-70% of the daily calorie intake of carbohydrates (mostly slowly absorbed), 15-20% of proteins and 10-15% of lipids.

Diet is therefore hyperglycidic, hypolipidic and normoproteic; this because gluconeogenesis in GSD type I is not effective, since the final compound, which is glucose-6-phosphate, cannot be utilized as a source of glucose.

This also explains why in GSD type I galactose and fructose intake should be restricted, this being the crucial point of the dietary qualitative protocol.

Since during the first two years of life administration of uncooked corn starch is not advisable because amilase enzymatic activity might be still immature, nocturnal continuous nasogastric infusion [22] is recommended as the only alternative to feeding children every three hours even at night.

It consists in providing special milk formulas supplemented with glucose polymers during the overnight 12 hours through a nasogastric tube properly located. This guarantees an overnight normoglycaemia, allowing children to sleep normally. It should provide about 35% of the daily caloric intake and should start not later than 1 hour after the last meal: the tube should then be removed not earlier than 15 minutes before the first meal in the morning. The volume of food must be controlled accurately by a paediatric enteral pump and great care must be taken to avoid accidental withdrawal (tube displacement, power failure) of the continuous carbohydrate intake.

When well tolerated, nocturnal nasogastric feeding should be prolonged to the end of adolescence, when the somatic development has been completed.

In the case children and their families refuse this kind of feeding, even because they are psychologically disturbed, administration of uncooked cornstarch [23] represents a useful alternative. Among different kinds of starch, uncooked cornstarch is the most effective in maintaining normoglycaemia for 6-8 hours after meals.

It should be administered1/2-1 hour after a meal at a starting dose of 0.5 g/kg, which can be progressively increased to 2.0 g/kg. Cornstarch can be mixed with water or milk.

If cornstarch is well tolerated, it allows children to have a nocturnal interval of 6 hours between two meals, reducing the total number of daily meals to 5 including one at night.

Usually in children with a good metabolic control, biochemical alterations are restored to norm; however a pharmaceutical intervention (allopurinol) is sometimes needed to help prevent hyperuricemia as well as antilipidaemic drugs may be helpful to contrast hyperlipidaemia [24]. With regard to this, we recently introduced a dietary supplementation with long chain polyunsaturated fatty acids which seems to be very effective. However, their supply deserves careful attention

for their secondary effects on blood coagulation and on the possible development of liver malignancies; with regard to this, a simultaneous and appropriate intake of anti-oxidant compounds is needed.

Other types of GSD, namely GSD type III and VI, may cause hypoglycaemia, hepatomegaly and hyperlipidaemia, although the clinical picture is usually milder compared to GSD type I.

In this forms, glucose cannot be released by breakdown of glycogen, but it can be normally produced by the neoglucogenesis pathways from amino acids and other carbohydrates.

A high protein diet with frequent meals, but without a qualitative carbohydrate restriction is therefore indicated.

Galactosemia

Three major enzymatic defects are associated with galactose metabolism: a) deficiency of galactose 1-phosphate uridyltransferase required to metabolize galactose to glucose (classical form of galactosemia); b) deficiency of galactokinase which catalyses the formation of galactose-1-phosphate from galactose; c) deficiency of UDP-galactose-4 epimerase, which leads to UDP-glucose formation.

Biochemical findings include raised serum and urine galactose with depressed blood glucose levels and raised galactose-1-phosphate in erythrocytes, after the child has been fed milk (human, or infant formula as dietary source of galactose).

Classically, galactosemia usually presents as poor suckling, failure to thrive, vomiting, diarrhoea, jaundice and hepatomegaly. If not treated, it can be fatal, but if the child survives without treatment he develops mental retardation, cirrhosis of the liver and cataracts.

This picture is usually caused by galactose-1-phosphate uridyltransferase deficiency, while it is usually milder in the epimerase deficiency. Galactokinase deficient patients usually present only cataracts.

Early diagnosis and prompt dietary treatment can lead to excellent immediate results and to a favourable long-term prognosis, although some patients may develop major or minor complications despite a good dietary compliance.

Therapy is based on dietary exclusion of galactose and lactose to be prolonged for the whole life [25]. Milk and dairy products are a major source of lactose; however, many other foods are very rich in galactose such as spinach, cocoa, whole soy, liver, kidney, brain, eggs, and should therefore be excluded from diet.

Table 7. - Allowed and forbidden natural foods for children affected by galactosaemia

Foods	Allowed	Forbidden
Meat, fish, poultry	Veal, chicken, turkey, lamb, pork and ham, shellfish	Meat, fish or poultry dishes, made up with cream, milk, butter, sausages, burgers, liver sausages, brain, liver
Milk and dairy products	No one, except those lactose-free	All kinds of milk or milk containing food, even if evaporated, skimmed, non-fat milk, yogurth, cheese, ice-creams, creams
Eggs	All	
Legumes	All	
Cereals	Wheat, rice, corn, semolina, bread, corn-flakes, macaroni	Egg-noodles, cereals fortified with milk or dairy products
Vegetables	All vegetables without butter, milk products, potatoes	Peas and other vegetables or potatoes cooked with milk, cream or butter
Fruit	All varieties, fruit juices without lactose, nuts, olives	
Cakes and sweets	All known to be lactose free, cocoa	All known to contain lactose, milk chocolate
Fats	Margarins, vegetable oils	Milk-containing margarins, butter

Until the age of weaning, children are fed milk-formula free of lactose, while afterwards parents are usually given a list of permitted and forbidden foods, in order to have more dietary choices (Table 7).

Calcium supplementation should be provided in order to prevent secondary deficiency due to milk and dairy product restrictions. Therapy should then be prolonged for life, with periodical clinical (with height and weight measurements) and biochemical controls (urinary and plasma galactose and, most important, galactose-1-phosphate estimation in erythrocytes).

Despite an early introduced and well-controlled diet, some clinical abnormalities may occur, such as cataracts or reduced growth rate in comparison to children of similar age.

However the most concerning complications are some differences between IQ and function, learning difficulties and distractability, reported in children still on well-controlled diet [26]. Although a possible damaging effect on the fetus by mother lactose intake during pregnancy has been claimed, galactose-1-phosphate concentration was found to be high in cord blood erythrocytes of fetuses whose mothers were on a restricted lactose intake throughout pregnancy. This suggests that the fetus of heterozygote mothers is exposed to this "toxic" metabolite in intrauterine life too.

Life-long galactose restricted diet still represents the basic therapy also for the other forms of galactosemia, although minor clinical features are usually present.

Submitted on invitation.
Accepted on 23 May 1995.

REFERENCES

1. ELSAS, L.J. & ACOSTA, P.B. 1988. Nutrition support of inherited metabolic diseases. In: *Modern nutrition in health and disease.* M.E. Shils & V.R. Young (Eds). Lea & Febiger, Philadelphia. pp. 1337-1379.

2. KOCH, R. & WENZ, E. 1987. Phenylketonuria. *Ann. Rev. Nutr.* **7**: 117-135.

3. KAUFMAN, S. 1989. An evaluation of the possible neurotoxicity of metabolites of phenylalanine. *J. Pediatr.* **114**: 895-900.

4. PARDRIDGE, W.M. & CHOI, T.D. 1986. Neutral amino acid transport at the blood-brain barrier. *Fed. Proc.* **45**: 2073-2078.

5. HOMMES, F.A., ELLER, A.G. & TAYLOR, E.H. 1982. Turn-over of the fast components of myelin an myelin proteins in experimental hyperphenylalaninemia. Revelance to termination of dietary treatment in human PKU. *J. Inher. Metab. Dis.* **5**: 21-25.

6. HOMMES, F.A. & MATSUO, K. 1987. Effect of phenylalanine on brain maturation. In: *Dietary phenylalanine and brain function.* R.J. Wurtman & E. Ritter Walker (Eds). Washington, D.C.

7. BLAU, N., NIEDERWIESER, A. & CURTIUS, H. CH. 1990. Eleven years of screening of tetrahydrobiopterin deficiency: the Zurich experience. *Ped. Res.* **305**: abs. 163.

8. GIOVANNINI, M., LONGHI, R., RIVA, E., CERONE, R. & BURLINA, A. 1985. Protocollo per la dietoterapia delle iperfenilalaninemie. Gruppo di studio di Nutrizione della Società Italiana di Pediatria. *Riv. Ital. Pediatr.* **11**: 434-439.

9. DEPONDT, E., OGIER, H., MUNNICH, A. & SAUDUBRAY, J.M. 1983. Le système de parts ponderales. *Arch. Fr. Pediatr.* **40**: 251-256.

10. RIVA, E., AGOSTONI, C., BIASUCCI, G., CESA-BIANCHI, A., ROTTOLI, A. & GIOVANNINI, M. 1993. Nutritional follow-up in treated hyperphenylalaninemias. *Int. Pediatr.* **8** (1): 25-30.

11. SOCIETA' ITALIANA DI NUTRIZIONE UMANA. 1987. *Livelli di assunzione giornalieri raccomandati di energia e nutrienti per la popolazione italiana. Revisione 1986-'87.* Istituto Nazionale della Nutrizione, Roma.

12. LONGHI, R., ROTTOLI, A., VITTORELLI, A., ZECCHINI, G., BONABITACOLA, T., BERTASSI, F., RIVA, E. & GIOVANNINI, M. 1987. Trace elements nutriture in hyperphenylalaninemic patients. Long-term follow-up study. *Eur. J. Pediatr.* **146** (Suppl. 1): A32-A37.

13. AGOSTONI, C., RIVA, E., VALSASINA, R., BELLU', R., GHIGLIONI, D. & GIOVANNINI, M. 1990. Plasma and urine levels of taurine in PKU children and in normal control population. In: *Abstract book 5th International congress of inborn errors of metabolism.* Asilomar, Pacific Grove, CA, USA.

14. GIOVANNINI, M., AGOSTONI, C. & SALARI, P.C. 1991. Is carnitine essential in children? *J. Int. Med. Res.* **19**: 88-102.

15. GALLUZZO, C., ORTISI, M.T., CASTELLI, L., AGOSTONI, C. & LONGHI, R. 1985. Plasma lipid concentrations in 42 treated phenylketonuric children. *J. Inher. Metab. Dis.* **8** (Suppl. 2): 129.

16. GALLI, C., AGOSTONI, C., MOSCONI, C., RIVA, E., SALARI, P.C. & GIOVANNINI, M. 1991. Reduced plasma C-20 and C-22 polyunsaturated fatty acids in PKU children under dietary intervention. *J. Pediatr.* **114**: 562-567.

17. NEURINGER, M. & CONNOR, W. 1986. N-3 fatty acids in the brain and retina: evidence for their essentiality. *Nutr. Rev.* **44**: 285-294.

18. GIOVANNINI, M., AGOSTONI, C., GALLUZZO, C., BELLU', R., ORTISI, M.T. & RIVA, E. 1988. Low serum concentrations of immunoglobulins G, A and M in children on low antigenic charge diets. *Acta Paediatr. Scand.* **77**: 306-307.

19. GIOVANNINI, M., BIASUCCI, G. & AGOSTONI, C. 1994. Fatty acid supplementation in a case of maternal phenylketonuria. *J. Inher. Metab. Dis.* **17**: 630-631.

20. FRANCIS, D.E.M. 1987. Dietary management of disorders of amino acid metabolism, organic acidaemias and urea cycle defects. In: *Diets for sick children.* 4th ed. Blackwell Scientific Publications Ed., Oxford. pp. 263-312.

21. MOSES, W.S. 1990. Pathophysiology and dietary treatment of the glycogen storage disease. *J. Pediatr. Gastrenterol. Nutr.* **11**: 155-174.

22. GREEN, H.L., SLONIM, A.E., O'NEIL, J.A. & BURR, I.M. 1976. Continuous nocturnal intragastric feeding for the management of type I glycogen storage disease. *N. Engl. J. Med.* **194**: 423-425.

23. CHEN, Y.T., CORNBLATH, M. & SIDBURY, J.B. 1984. Cornstarch therapy in type I glycogen storage disease. *N. Engl. J. Med.* **310**: 171-175.

24. AGOSTONI, C., SALARI, C., FLUMINE, P., TROJAN, S., BELLU', R., LONGHI, R., ROTTOLI, A. & RIVA, E. 1992. Incrementata sintesi di lipidi e acidi grassi in soggetti affetti da glicogenosi Ia e Ib in terapia dietetica. *Riv. Ital. Pediatr.* **18**: 549-554.

25. BURLINA, A. & LONGHI, R. 1989. Protocollo per la dietoterapia della galattosemia. Gruppo di studio di Nutrizione della Società Italiana di Pediatria. *Riv. Ital. Pediatr.* **15**: 340-343.

26. WAISBREN, S.E. & NORMAN, T. 1983. Speech and language defects in early treated children with galactosemia. *J. Pediatr.* **102**: 75-78.