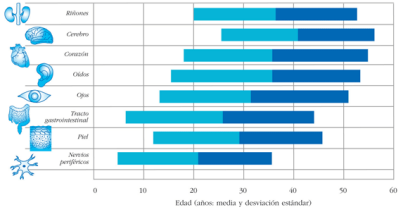
EGM: DE LA PEDIATRÍA A LA EDAD ADULTA

Dr. Luis Aldamiz-Echevarría
Unidad de Metabolismo
Sº de Pediatría. Hospital Universitario Cruces

Proceso asistencial

Diagnóstico



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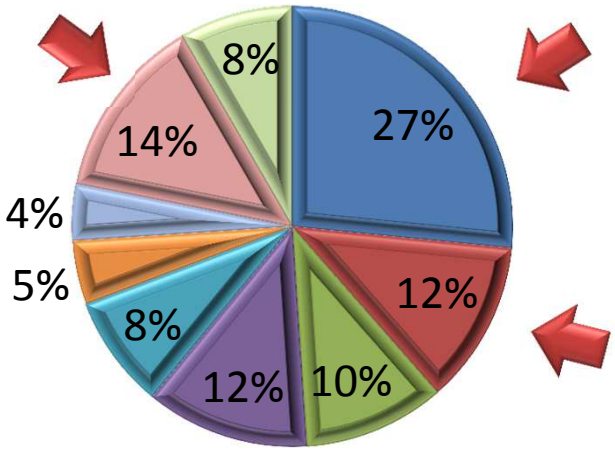
Prevalencia de los EIM

$$P = \frac{Ct}{Nt}$$



- PKU/HPA
- Acidemia Organica
- Def Ciclo de la Urea
- Mitocondriales
- Varias
- Tirosinemia
- b-Oxidacion
- Lisosomales
- Hidratos carbono

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Una historia natural conocida, ¿Está todo dicho?

Fenilcetonuria

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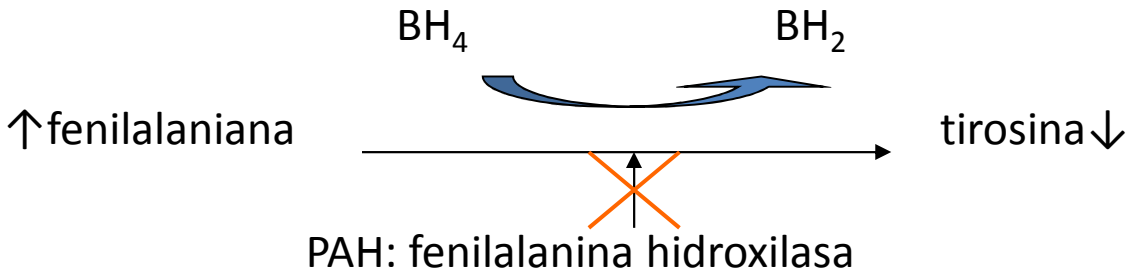
Fenilcetonuria: deficiencia de PAH



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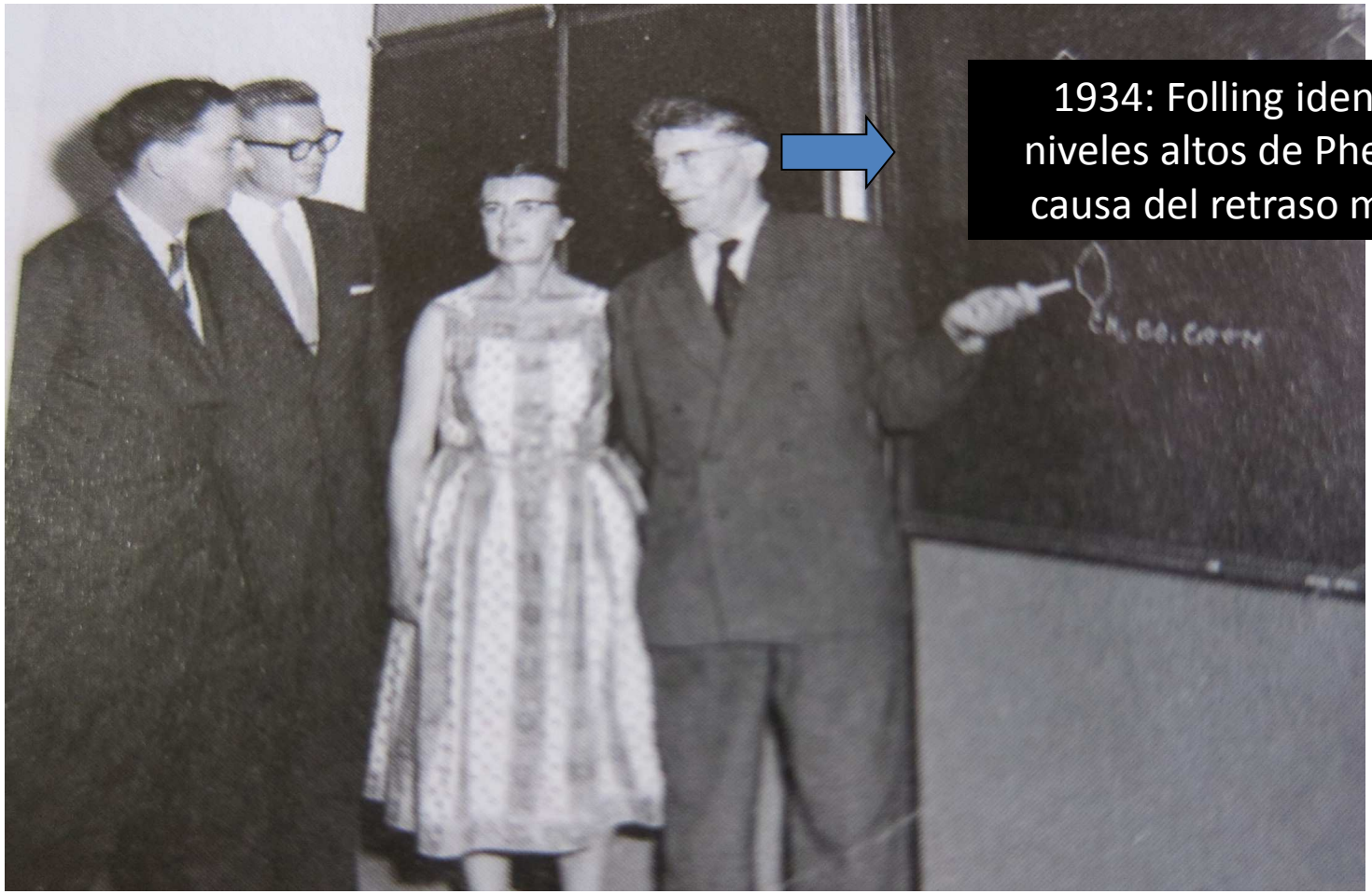
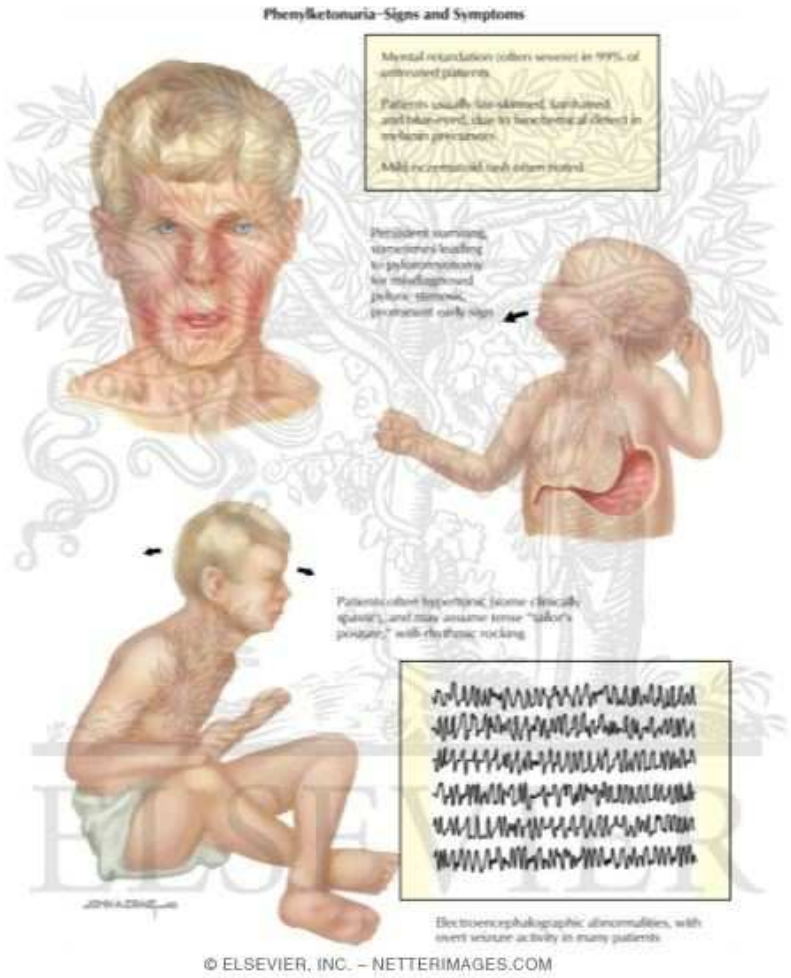
Historia



1934: Folling identificó niveles altos de Phe como causa del retraso mental.

Fenotipo de la PKU

- Convulsiones, ataxia, problemas de comportamiento
- Retraso mental
- Pelo rubio, ojos claros



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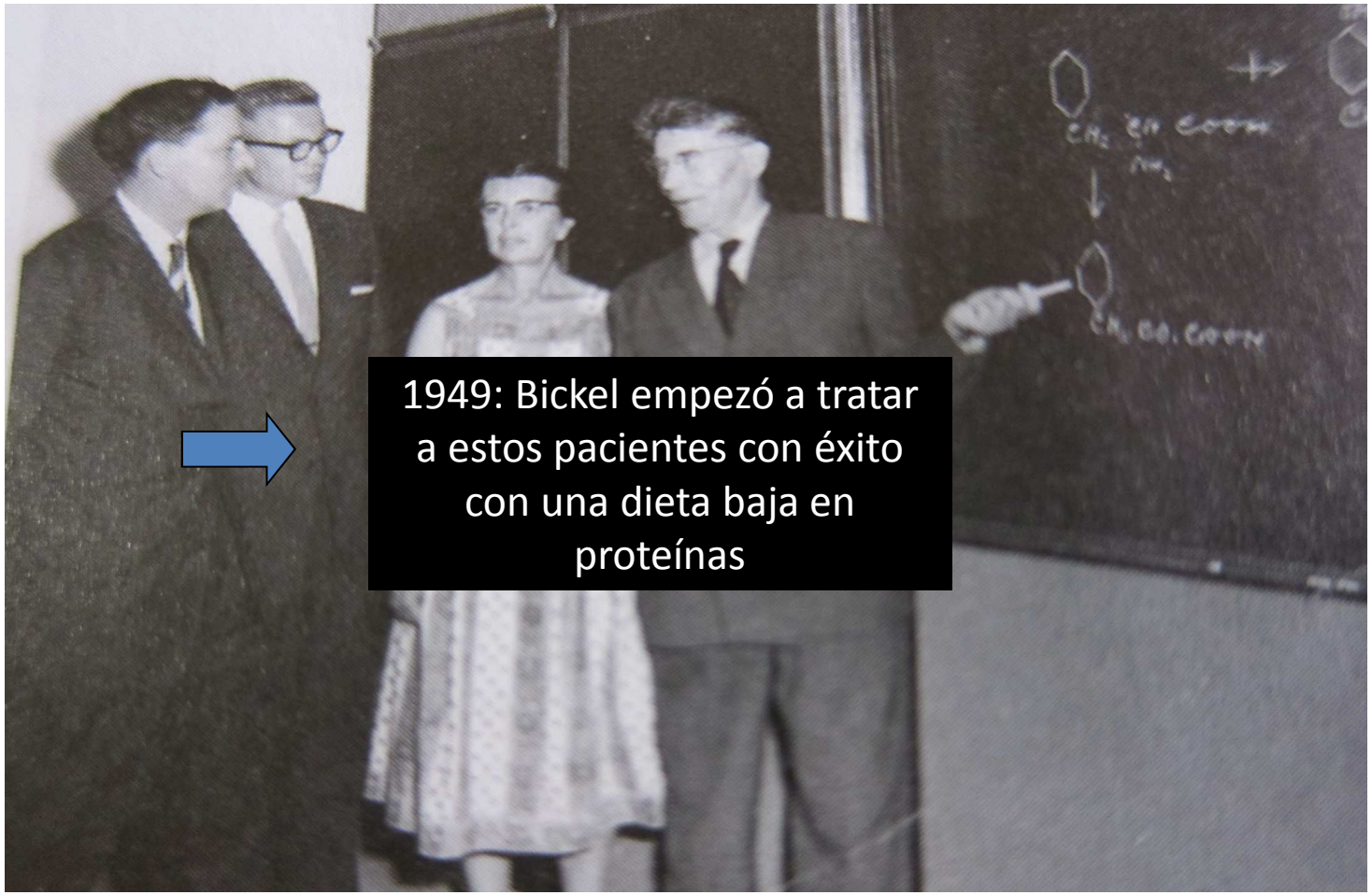
Historia


1949: Bickel empezó a tratar a estos pacientes con éxito con una dieta baja en proteínas

Tratamiento: dieta baja en proteínas

Alimentos especiales bajos en proteinas: pasta, arroz, galletas…

Producto PKU

Aminoácidos exento Phe

SUPLEMENTADA
Tyr, vitaminas, oligoelementos, ácidos grasos esenciales

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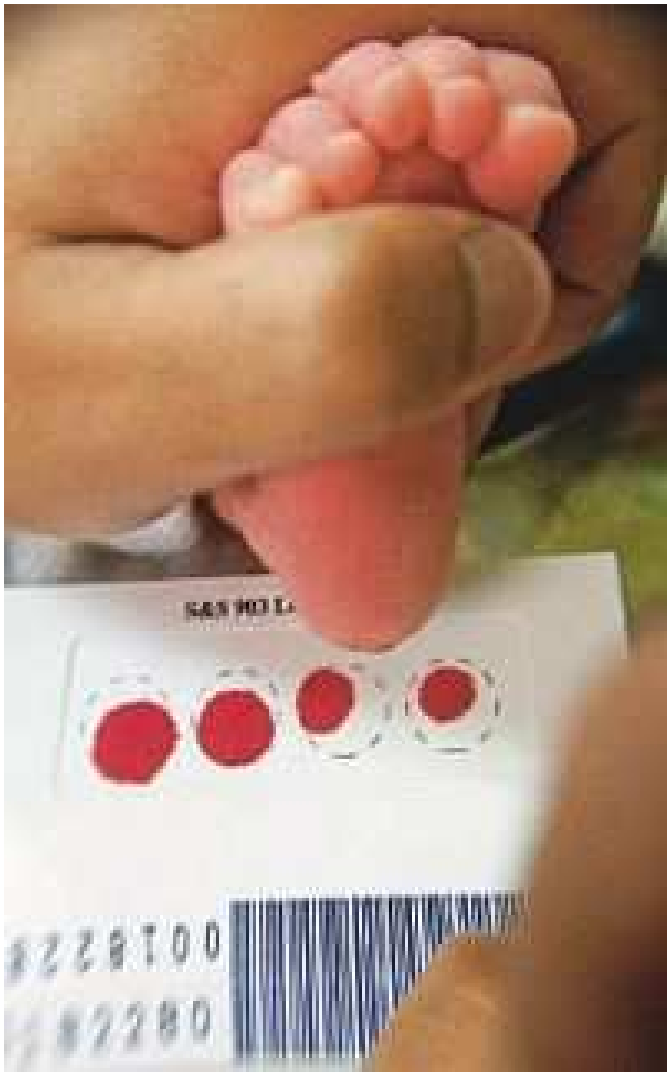
Historia

1963: Guthrie desarrolla técnica medir niveles de Phe en cartón impregnado



Nuevo fenotipo de la PKU

MAYORES DE 18 AÑOS

	%	Trabajo
Licenciatura universitaria	44	Actualmente estudiando
Grado superior F.P.	28	Todos
Bachiller	-	
ESO	14	No
No	14	Taller protegido

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Genetics inMedicine | ACMG PRACTICE GUIDELINES

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Phenylalanine hydroxylase deficiency: diagnosis and management guideline

Jerry Vockley, MD, PhD[1,2], Hans C. Andersson, MD[3], Kevin M. Antshel, PhD[4], Nancy E. Braverman, MD[5], Barbara K. Burton, MD[6], Dianne M. Frazier, PhD, MPH[7], John Mitchell, MD[5], Wendy E. Smith, MD[8], Barry H. Thompson, MD[9] and Susan A. Berry, MD[10]; For the American College of Medical Genetics and Genomics Therapeutic Committee

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical services. Adherence to this guideline is completely voluntary and does not necessarily assure a successful medical outcome. This guideline should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians are also advised to take notice of the date this guideline was adopted and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

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Target blood Phenylalanine concentrations (µmol/L) in PKU patients in European countries

	< 2 years	2-6 years	7-9 years	10-12 years	13-15 years	> 16 years
Austria	40-240	40-240	40-240	40-900	40-900	40-1200
Croatia	130-240	130-360	130-360	130-600	130-600	130-960
Denmark	120-300 (<4 years)	120-400 (4-8 years)	120-600 (8-10 years)	120-700	120-900	120-900
France	120-300	120-300	120-300	120-600	120-900	120-1200
Germany	40-240	40-240	40-240	40-900	40-900	40-1200
Hungary	120-360	120-360	120-480	120-480	120-480 (7-14 years)	120-600 (>14 years)
Italy	120-360	120-360	120-360	120-360	120-600	120-600
Netherlands	120-360	120-360	120-360	120-360	120-600	120-600
Poland	120-360	120-360	120-360	120-720	120-720	120-720
Portugal	120-360	120-360	120-360	120-360	120-480	120-480
Spain	<360	<360	<480	<480	<720	<720
Turkey	60-240	60-240	60-240	60-240	60-240	60-240
UK	120-360	120-360	120-480	120-480	120-700	120-700

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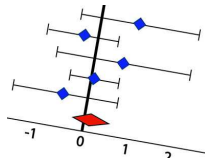
E.S.PKU

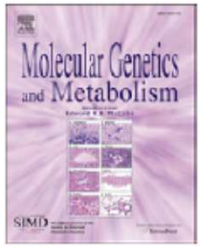


Molecular Genetics and Metabolism 101 (2010) 99–109

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Minireview

Suboptimal outcomes in patients with PKU treated early with diet alone: *Revisiting the evidence*

G.M. Enns [a,*], R. Koch [b], V. Brumm, E. Blakely [c], R. Suter [d], E. Jurecki [d]

[a] *Division of Medical Genetics, Department of Pediatrics, Lucile Packard Children's Hospital, Stanford University, Stanford, CA, USA*
[b] *University of Southern California/Keck School of Medicine, Los Angeles, CA, USA*
[c] *University of Rochester, Rochester, NY, USA*
[d] *BioMarin Pharmaceutical Inc., Novato, CA, USA*

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Infants	Children/Adolescents*	Adults*	Seniors
► reduction of long-chain polyunsaturated fatty acid (LCPUFA) status [4,96,108] ► deficits in cognitive functioning/abilities** [4,45]	► white matter abnormalities [7,8,73,78,89,92] ► brain volume abnormalities [92] ► intracellular cerebral accumulation of a hydrophili metabolite [85] ► reduced erythrocyte-membrane AChE activity [86] ► deficits in cognitive functioning/abilities** [5-12,18-34,38-43,51,54,56,57,59-61,99,104] ► linear growth impairment [98,103,105] ► reduced head circumference [105] ► overweight [94] ► elevated total homocysteine levels [106,115,117] ► increased plasma lipid peroxidation [102,118] ► low antioxidant status [116,118] ► reduction of long-chain polyunsaturated fatty acid (LCPUFA) status [38,39,99-101,114,119] ► higher rates of internalizing problems and/or psychiatric treatment [35,36,43,53,58] ► increased behavioral problems, learning difficulties or reduced school achievement [11,14,26,53,55] ► reduced positive emotions [40] ► vitamin B(12) and/or vitamin B(6) deficiency [115] ► reduced markers for bone formation [126,129,132] ► reduced peak bone mass/bone density [133] ► reduced zinc levels [103] ► reduced selenium levels [104] ► iron deficiency [95, 97] ► reduced carnitine levels [120]	► white matter abnormalities [13,37,49,69,70,73,75, 77-79,82,87,88,91] ► grey matter abnormalities [70,82] ► brain volume abnormalities [69,71,82,83] ► decreased cerebral functional connectivity [68] ► deficits in cognitive functioning/abilities** [5,13,15-17,19,21-23,37,44,46-50,57,68,70,73] ► reduced cerebral protein synthesis rate [72] ► increased body mass index (BMI), overweight [110] ► increased brain phenylalanine levels [74,80,81,88] ► elevated cholesterol/HDL ratios [111] ► reductions of long-chain polyunsaturated fatty acids (LCPUFA) [111,119] ► reduced cerebral glucose metabolic rates [90] ► imbalances of cerebral energy metabolism [84] ► intracellular cerebral accumulation of a hydrophilic metabolite [85] ► vitamin B(12) and/or vitamin B(6) deficiency [107,113] ► behavioral problems [37,53,55] ► reduced achievement [37,55] ► increased agitation [65] ► reduced positive emotions, delayed autonomy [52] ► increased anxiety and depressiveness [64] ► reduced cerebral fluoro-L-dopamine uptake [76] ► reduced bone formation [128,130,132,134] ► reduced peak bone mass/bone density [131] ► elevated total homocysteine levels [107] ► altered folate metabolism [109] ► reduced platelet serotonin levels [112] ► increased Plasma lipid peroxidation [118] ► low antioxidant status [118] ► reduced carnitine levels [120]	► TBD (early-treated patients through newborn screening are now in their 40s; therefore, long-term repercussions of diet management are still under debate)

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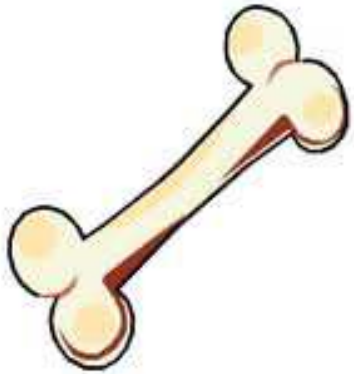
J Inherit Metab Dis
DOI 10.1007/s10545-010-9189-0

RESEARCH REPORT

Fatty acid profile in patients with phenylketonuria and its relationship with bone mineral density

Sergio Lage · María Bueno · Fernando Andrade · José Ángel Prieto · Carmen Delgado · María Legarda · Pablo Sanjurjo · Luis Jose Aldámiz-Echevarría



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Molecular Genetics and Metabolism 108 (2013) 149–154

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Risk factors for developing mineral bone disease in phenylketonuric patients

Alicia Mirás [a], M. Dolores Bóveda [b], María R. Leis [c], Antonio Mera [d], Luís Aldámiz-Echevarría [e], José R. Fernández-Lorenzo [f], José M. Fraga [a], María L. Couce [a,*]

[a] Unit of Diagnosis and Treatment of Congenital Metabolic Diseases, Department of Pediatrics, Hospital Clinico Universitario de Santiago, Travesía da Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain
[b] Unit of Diagnosis and Treatment of Congenital Metabolic Diseases, Metabolic Laboratory, Hospital Clinico Universitario de Santiago, Travesía da Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain
[c] Unit of Nutrition and Metabolism, Department of Pediatrics, Hospital Clinico Universitario de Santiago, Travesía da Choupana s/n,15706 Santiago de Compostela, A Coruña, Spain
[d] Rheumatology Service, Hospital Clinico Universitario de Santiago, Travesía da Choupana s/n, 15706 Santiago de Compostela, A Coruña, Spain
[e] Unit of Metabolism, Department of Pediatrics, Hospital de Cruces, Plaza de Cruces s/n, 48903, Barakaldo, Vizcaya, Spain
[f] Pediatric Service, Hospital Xeral Cíes, C/Pizarro 2, 36204 Vigo, Spain

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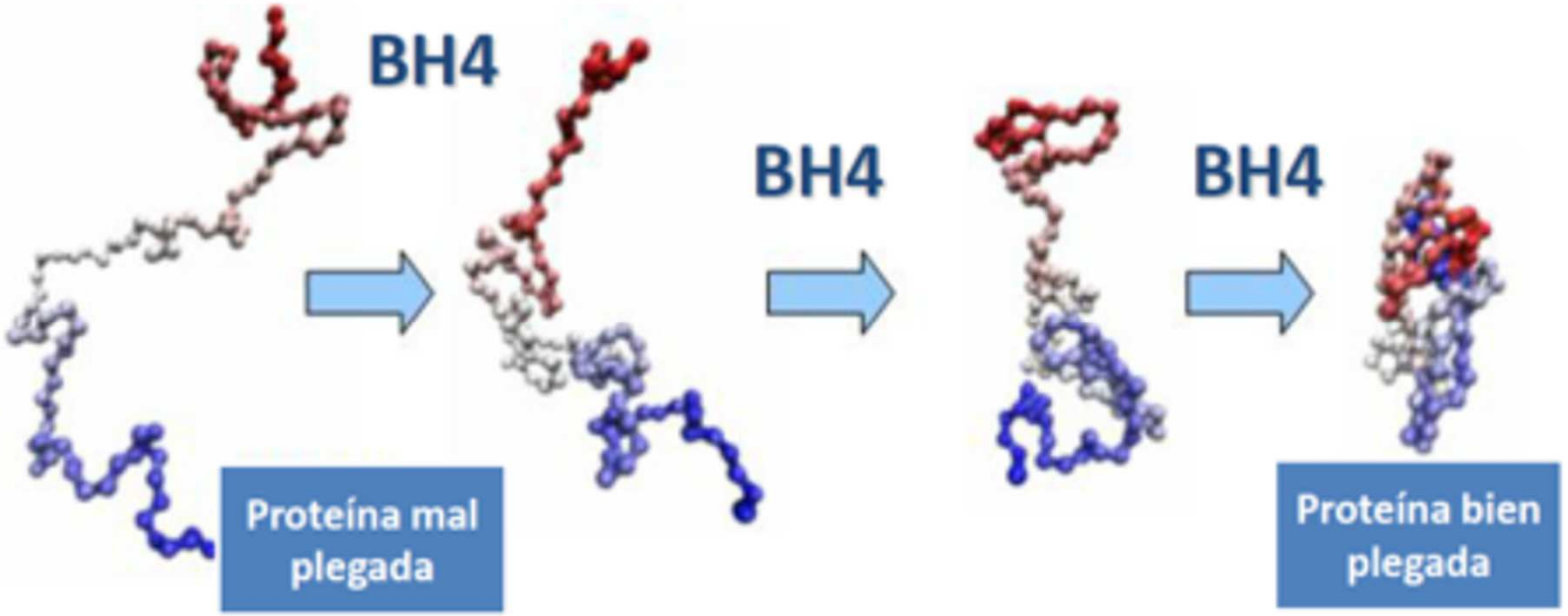
Sapropterina

La BH4 ayuda a plegar la proteína mutada e impide su degradación



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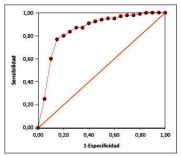
Efecto chaperona: mejora funcionamiento de PAH.
PKU leves-moderadas: mejor respuesta



METABOLISM CLINICAL AND EXPERIMENTAL 61 (2012) 1809–1816

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Methods

New evidence for assessing tetrahydrobiopterin (BH_4) responsiveness

María A. Bueno[a], *Sergio Lage*[b], *Carmen Delgado*[a], *Fernando Andrade*[b], *María L. Couce*[c], *Domingo González-Lamuño*[d], *Manuel Pérez*[a], *Luis Aldámiz-Echevarría*[b,*]

[a] *Metabolic Disorders, Dietetics and Nutrition Unit, Virgen del Rocío Teaching Hospital, s/n, 41013, Sevilla, Spain*
[b] *Division of Metabolism, Department of Paediatrics, Cruces Hospital, Plaza de Cruces s/n, 48903, Barakaldo, Vizcaya, Spain*
[c] *Metabolic Disorders Unit, Santiago de Compostela Teaching Hospital, Travesía da Choupana, s/n, 15706, Santiago de Compostela, La Coruña, Spain*
[d] *Paediatric Nephrology and Metabolism Unit, Marqués de Valdecilla Hospital, Valdecilla Avenue, 25, 39008, Santander, Cantabria, Spain*

Results. The 24-h test detected almost all BH_4 responders (30.3% of the 99 patients included in the analysis), with just two patients (2.0%) subsequently responding positively to the therapeutic test. The 24-h test did not give any false positive results.

Conclusions. The 24-h BH_4 loading test is clinically useful for screening phenylketonuric patients. Specifically, 95% of patients with Phe levels <700 μmol/L, and none with Phe levels >1500 μmol/L were BH_4-responsive. Given these results, we conclude that patients with Phe levels<700 μmol/L or>1500 μmol/L probably do not need to be tested, prioritising the identification of BH_4-responsiveness among individuals with intermediate Phe concentrations, between the aforementioned values. Additionally, our results suggest that the therapeutic test only needs to be performed in cases where the reduction in blood Phe levels after cofactor administration is within the range 40%–50%.

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Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Anthropometric characteristics and nutrition in a cohort of PAH-deficient patients

Luis Aldámiz-Echevarría [a,*], María A. Bueno [b], María L. Couce [c], Sergio Lage [a], Jaime Dalmau [d], Isidro Vitoria [d], Fernando Andrade [a], Javier Blasco [e], Carlos Alcalde [f], David Gil [g], María C. García [h], Domingo González-Lamuño [i], Mónica Ruiz [j], Luis Peña-Quintana [k], María A. Ruiz [l], David González [m], Felix Sánchez-Valverde [n]

Molecular Genetics and Metabolism 109 (2013) 331–338

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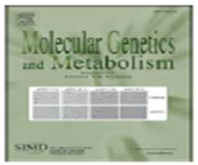
journal homepage: www.elsevier.com/locate/ymgme



Tetrahydrobiopterin therapy vs phenylalanine-restricted diet: Impact on growth in PKU

Luis Aldámiz-Echevarría [a,*], María A. Bueno [b], María L. Couce [c], Sergio Lage [a], Jaime Dalmau [d], Isidro Vitoria [d], Fernando Andrade [a], Marta Llarena [a], Javier Blasco [e], Carlos Alcalde [f], David Gil [g], María C. García [h], Domingo González-Lamuño [i], Mónica Ruiz [j], María A. Ruiz [k], David González [l], Felix Sánchez-Valverde [m]

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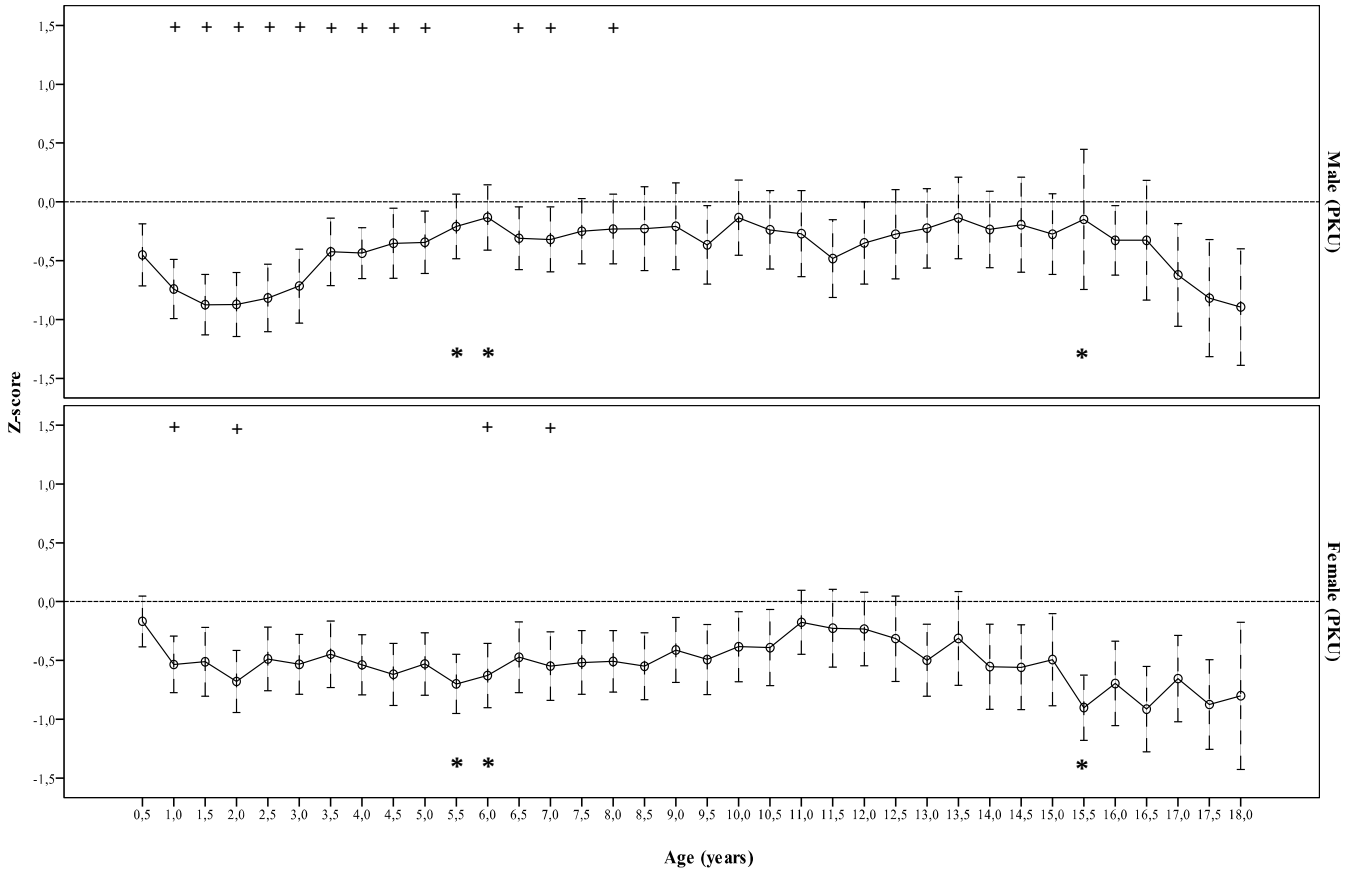
Evolución talla en PKU



ution of height Z-scores for patients with PKU from six months to eighteen years of age. (*) and (+) represent *p*-values < 0.05
ra-group (male *vs*. female) and inter-group (male/female-PKU *vs*. male/female mild-HPA) comparisons, respectively.

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Acta Pædiatr 91: 905–909. 2002

Taylor & Francis
healthsciences

Homocysteine and other vascular risk factors in patients with phenylketonuria on a diet

KH Schulpis, GA Karikas[1] and E Papakonstantinou

Institute of Child Health, and Pharmacokinetics and Parenteral Nutrition Unit[1], "Aghia Sophia" Children's Hospital, Athens, Greece

J Inherit Metab Dis (2012) 35:817–821
DOI 10.1007/s10545-011-9448-8

ORIGINAL ARTICLE

Free asymmetric dimethylarginine (ADMA) is low in children and adolescents with classical phenylketonuria (PKU)

M. Huemer · B. Simma · D. Mayr · D. Möslinger · A. Mühl · I. Schmid · H. Ulmer · O.A. Bodamer

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J Inherit Metab Dis
DOI 10.1007/s10545-012-9548-0

ORIGINAL ARTICLE

Chronic kidney disease in adolescent and adult patients with phenylketonuria

Julia B. Hennermann · Sylvia Roloff · Jutta Gellermann · Ilka Vollmer · Elke Windt · Barbara Vetter · Ursula Plöckinger · Eberhard Mönch · Uwe Querfeld

Received: 19 March 2012 / Revised: 13 September 2012 / Accepted: 4 October 2012
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Factores cardiovasculares

	Colesterol	Triglicéridos	Glucosa	Homocisteína	PCR
Dieta	148.2 (104-173)	73.0 (32-111)	84.8 (69-90)	8.7 (3.8-20.9)	0.24 (0.03-0.8)
BH4	156.5 (149-166)	70.7 (50-88)	92.6 (88-95)	6.9 (3.7-8.5)	0.45 (0.1-0.9)

	Vit B12	Ac Fólico	AMM orina
Dieta	638.9 (236-1307)	16.9 (6.6-24)	6.9 (1.2-20.0)
BH4	469.5 (312-665)	18 (10.7-24)	3.16 (1.5-6.3)

	Arginina	ADMA	Arg/ADMA	SDMA
Dieta	67.6 (39-87)	0.73 (0.6-1.1)	114.0 (86-143)	0.65 (0.4-0.8)
BH4	59.2 (33-70)	0.80 (0.7-0.8)	74.2 (56-103)	0.76 (0.7-0.8)

¿El cribado modifica la historia natural de un EIM del adulto?

Homocistinuria

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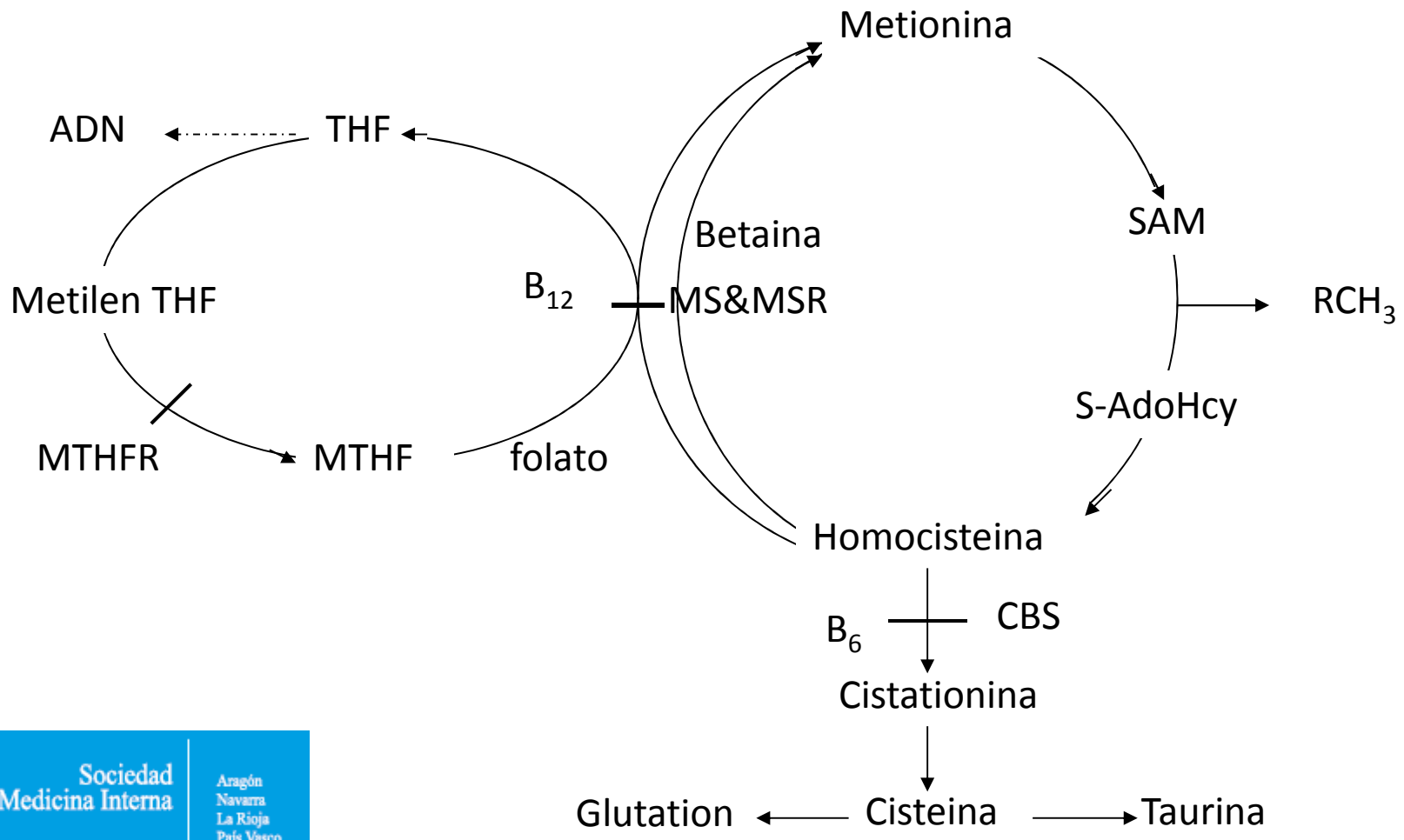
Metabolismo de la homocisteína



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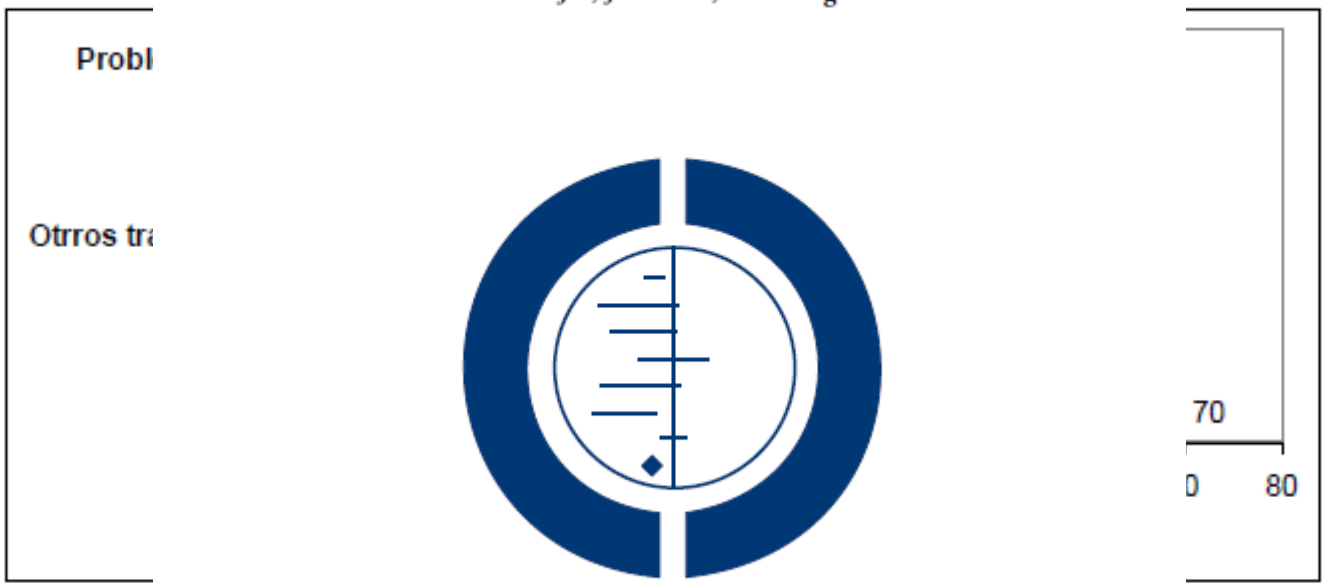
Homocistinuria

Newborn screening for homocystinuria (Review)

Walter JH, Jahnke N, Remmington T



THE COCHRANE COLLABORATION®

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Una historia natural con diferentes finales

Acidemia organica

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Enfermedad Glutarica tipo I

Características generales

(Kölker S. Pediatr Res 2006; 59: 840-847)

- Sobre 265 – 185 debutaron como crisis encefalica (70%), inicio insidioso (13%), y tardio (2%)
- La macrocefalia se da desde el nacimiento en el 74% de los casos en los de crisis encefalica
- El debut de la crisis encefalica es a los 9 meses (IC 95% 1-37 m)

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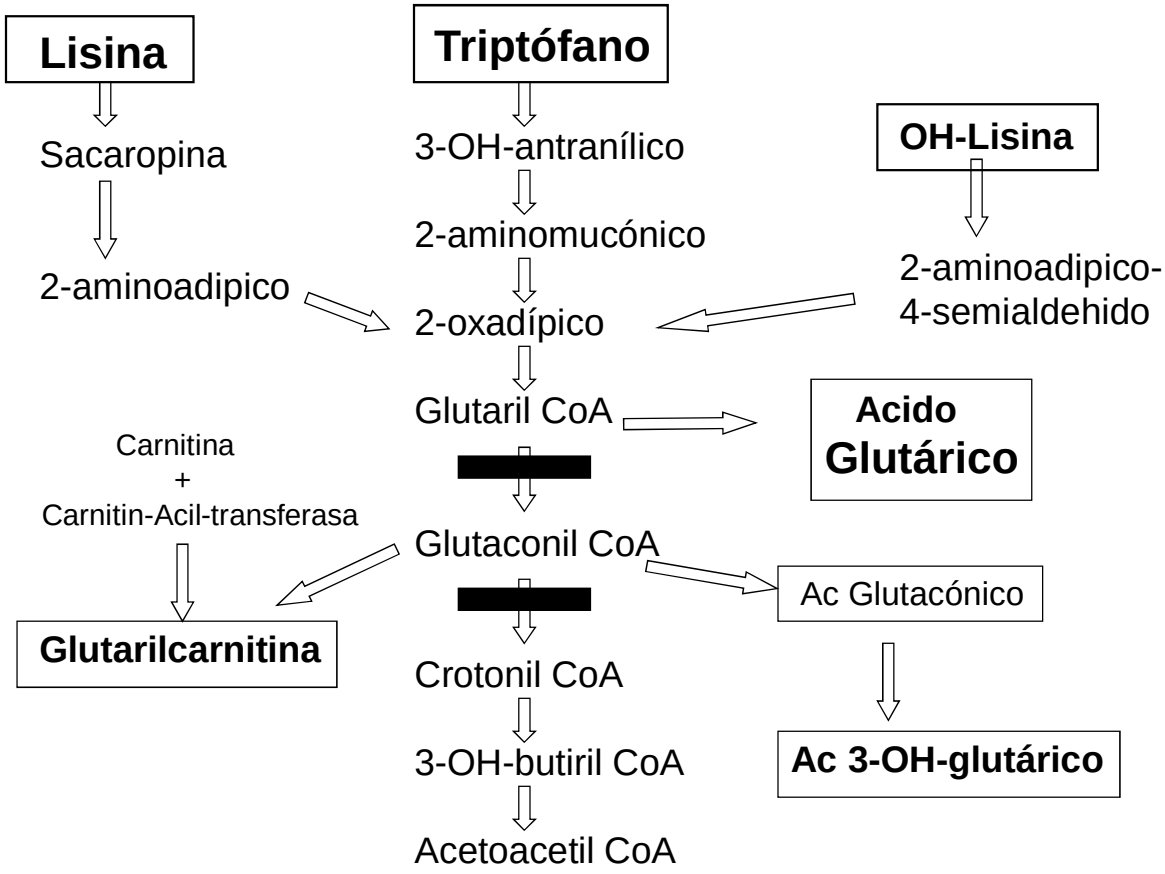
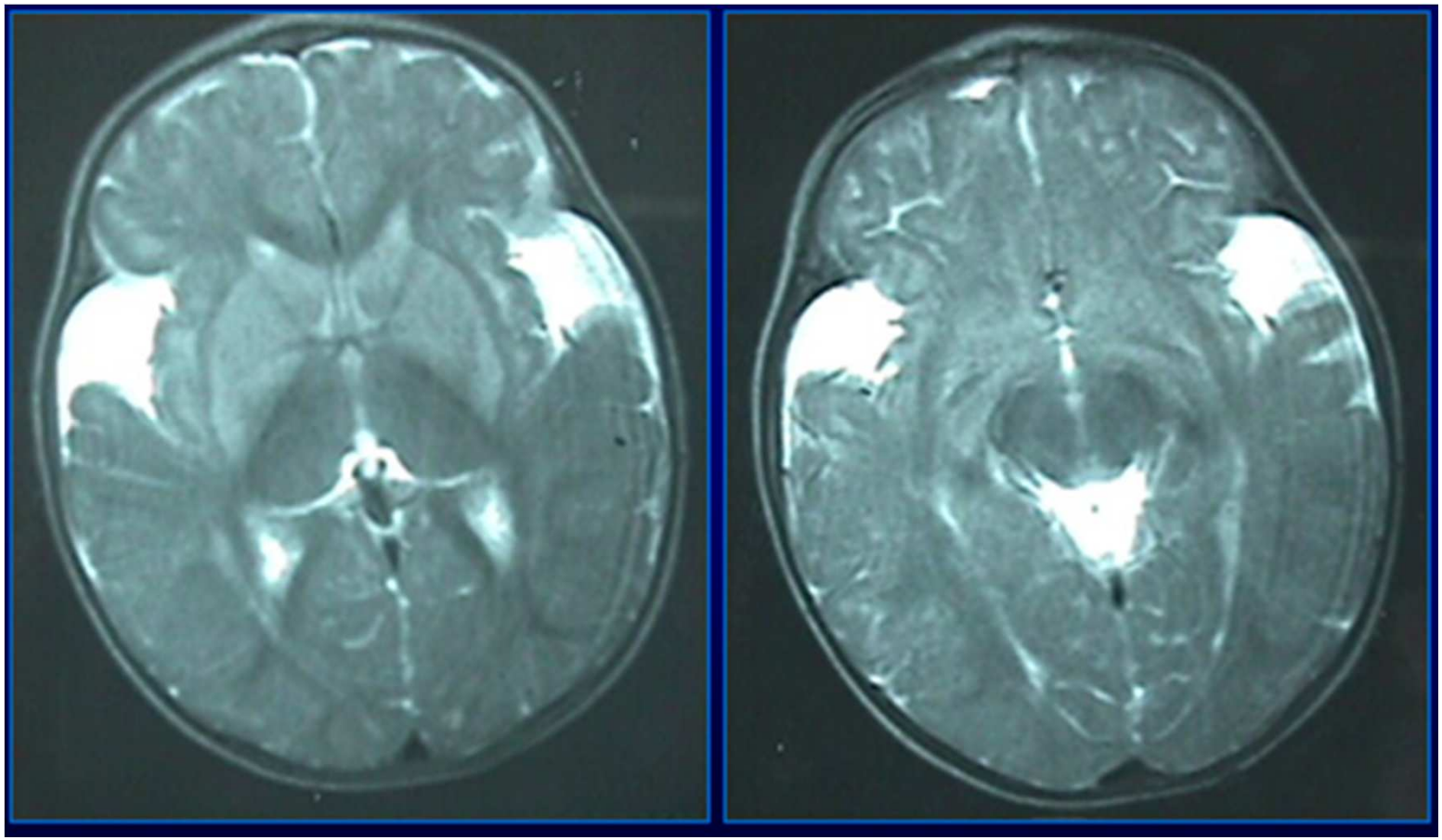

Lisina
Sacaropina
2-aminoadipico
Triptófano
3-OH-antranílico
2-aminomucónico
2-oxadípico
OH-Lisina
2-aminoadipico-
4-semialdehido
Glutaril CoA
Acido
Glutárico
Carnitina
+
Carnitin-Acil-transferasa
Glutarilcarnitina
Glutaconil CoA
Ac Glutacónico
Crotonil CoA
Ac 3-OH-glutárico
3-OH-butiril CoA
Acetoacetil CoA

GA1



Recomendaciones GA1

J Inherit Metab Dis (2007) 30:5–22
DOI 10.1007/s10545-006-0451-4

GUIDELINE

Guideline for the diagnosis and management of glutaryl-CoA dehydrogenase deficiency (glutaric aciduria type I)

S. Kölker · E. Christensen · J. V. Leonard · C. R. Greenberg · A. B. Burlina · A. P. Burlina · M. Dixon · M. Duran · S. I. Goodman · D. M. Koeller · E. Müller · E. R. Naughten · E. Neumaier-Probst · J. G. Okun · M. Kyllerman · R. A. Surtees · B. Wilcken · G. F. Hoffmann · P. Burgard

J Inherit Metab Dis (2011) 34:677–694
DOI 10.1007/s10545-011-9289-5

ORIGINAL ARTICLE

Diagnosis and management of glutaric aciduria type I – revised recommendations

Stefan Kölker · Ernst Christensen · James V. Leonard · Cheryl R. Greenberg · Avihu Boneh · Alberto B. Burlina · Alessandro P. Burlina · Marjorie Dixon · Marinus Duran · Angels García Cazorla · Stephen I. Goodman · David M. Koeller · Mårten Kyllerman · Chris Mühlhausen · Edith Müller · Jürgen G. Okun · Bridget Wilcken · Georg F. Hoffmann · Peter Burgard

Tratamiento

Statement #7. A low lysine diet (i.e., reducing lysine intake to a safe requirement) with or without additional administration of lysine-free, tryptophan-reduced amino acids supplements should be used for dietary treatment, in particular in asymptomatic patients up to age 6 years (grade C).

Statement #8. L-Carnitine should be supplemented in patients with glutaric aciduria type I and should be continued lifelong (grade C).

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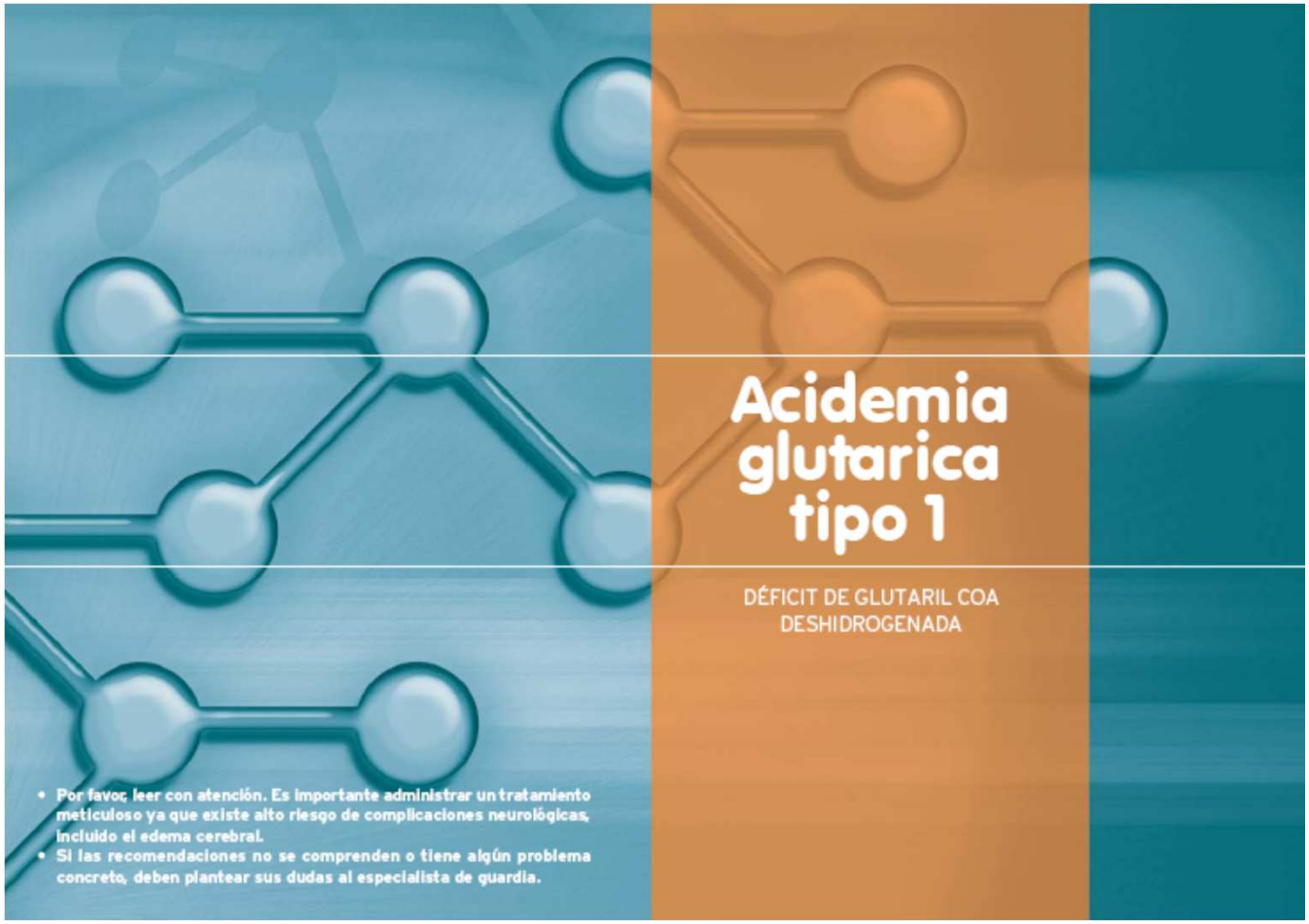
Tratamiento de emergencia

Statement #9. Emergency treatment should start without delay and should be performed aggressively during febrile illness, surgery and immunization within the vulnerable period for acute encephalopathic crises (up to age 6 years) (grade B).

Statement #10. Emergency treatment in children after age 6 years should be considered at least during severe illness. It should be performed similarly to that in the age group 0-6 years with adaptation to the individual (GCP).



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ORIGINAL ARTICLE

Use of Guidelines Improves the Neurological Outcome in Glutaric Aciduria Type I

Jana Heringer,[1] S. P. Nikolas Boy, MD,[1] Regina Ensenauer, MD,[2] Birgit Assmann, MD,[3] Johannes Zschocke, MD, PhD,[4] Inga Harting, MD,[5] Thomas Lücke, MD,[6,7] Esther M. Maier, MD,[2] Chris Mühlhausen, MD,[8] Gisela Haege, PhD,[1] Georg F. Hoffmann, MD,[1] Peter Burgard, PhD,[1] and Stefan Kölker, MD[1]

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ANN NEUROL 2010;68:743–752

Evolución de GA1

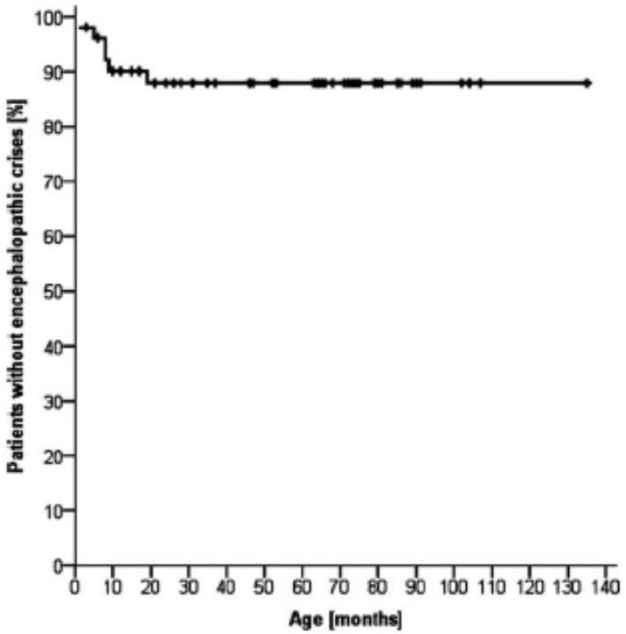

FIGURE 2: Acute encephalopathic crisis. In 11.5% of 52 neonatally diagnosed patients with glutaric aciduria type I, clinically apparent acute encephalopathic crises were precipitated by intercurrent infectious disease and occurred up to an age of 19 months. The figure presents the results of Kaplan-Meier analysis.

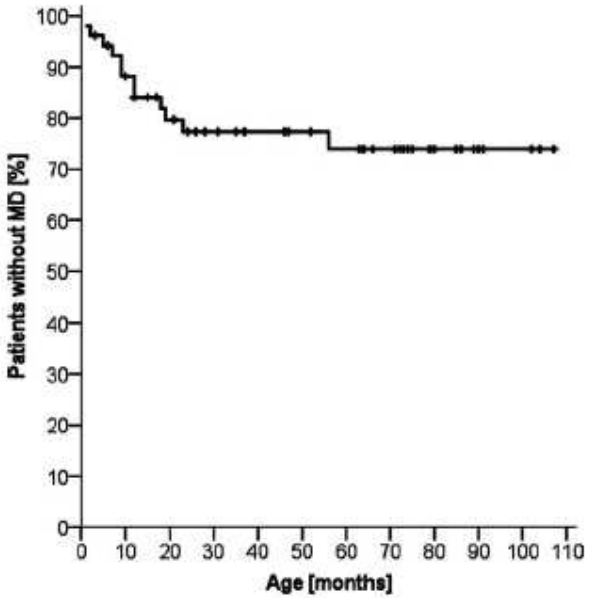

FIGURE 3: Movement disorder (MD) with predominant dystonia superimposed on axial hypotonia was found in 23% of 52 neonatally diagnosed patients with glutaric aciduria type I (11.5% severe, 11.5% mild), consequently also affecting patients without clinically apparent crises. The age at onset of dystonia showed a broader age range than for encephalopathic crises. The figure presents the results of Kaplan-Meier analysis.

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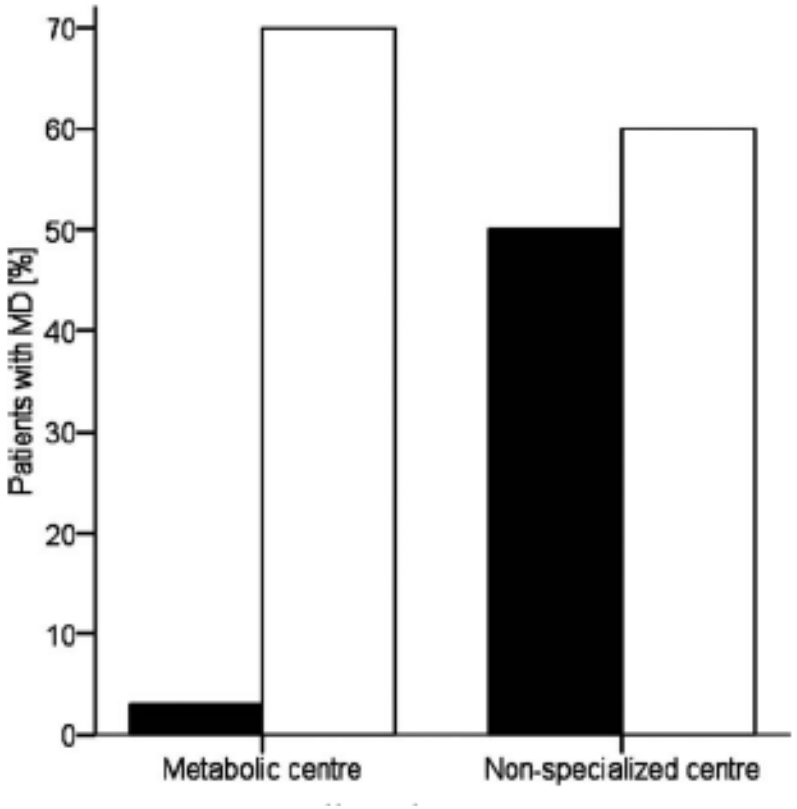
Evolución de GA1



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¿Un ECM en el embarazo?

Fenilcetonuria - Homocistinuria

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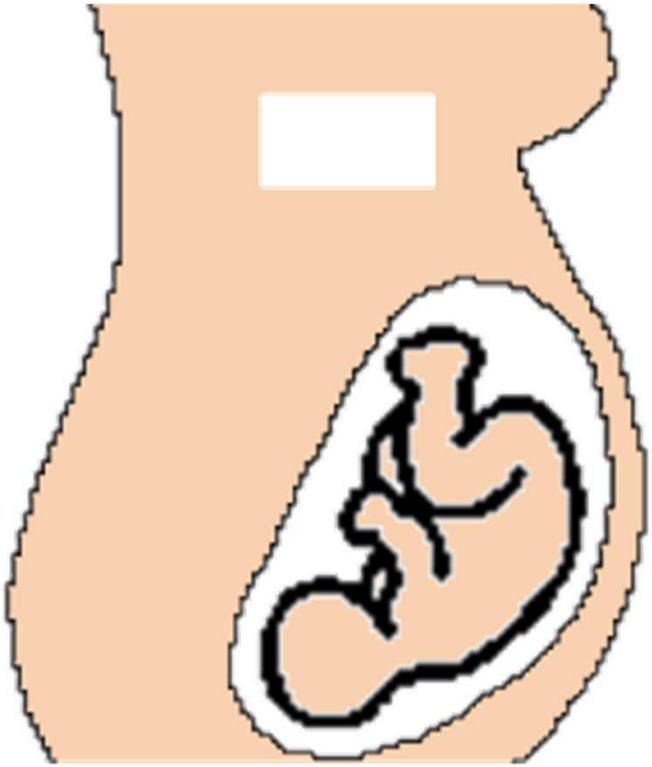
PKU materna

Es una embriofetopatía (afecta al embrión y al feto) que ocurre en hijos de madres con ↑fenilalanina

- *en formas moderadas de hiperfenilalaninemia(HPA)*
- *en la fenilcetonuria(PKU)*

que no han recibido el adecuado tratamiento dietético restringido en fenilalanina durante el embarazo.



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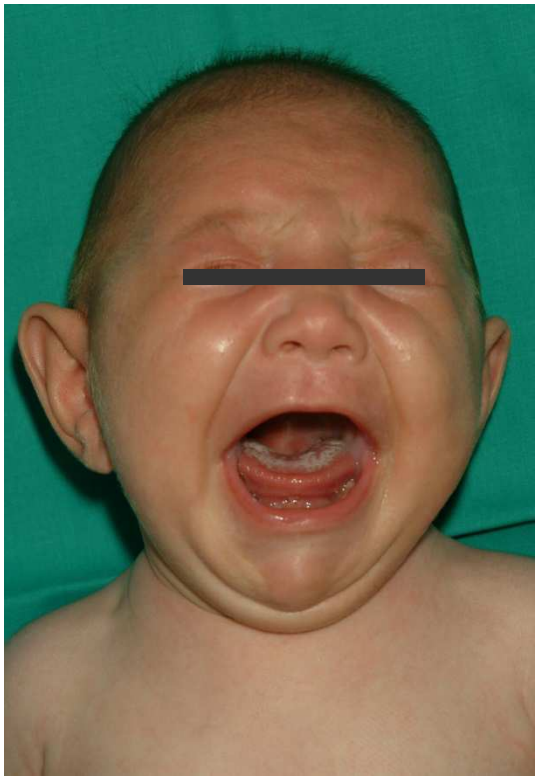
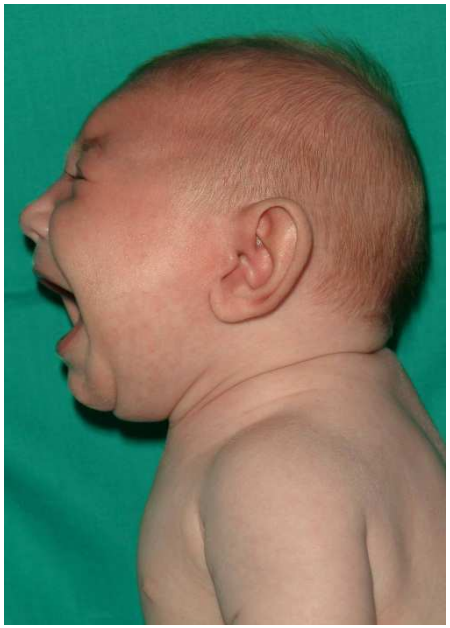
m-PKU: Presentación clínica



- Microcefalia
- Hipertelorismo
- < fisuras palpebrales
- Epicantus
- paladar ojival
- Micrognatia
- filtrum largo
- raíz nasal amplia-plana



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PKU materna

Para prevenir la embriofetopatía del hijo/a de una madre con fenilcetonuria hay que saber que:

"los efectos teratógenos son prácticamente nulos si se logran niveles de fenilalanina entre 100 y 250 µmol/L durante la gestación y desde los tres meses previos a la concepción

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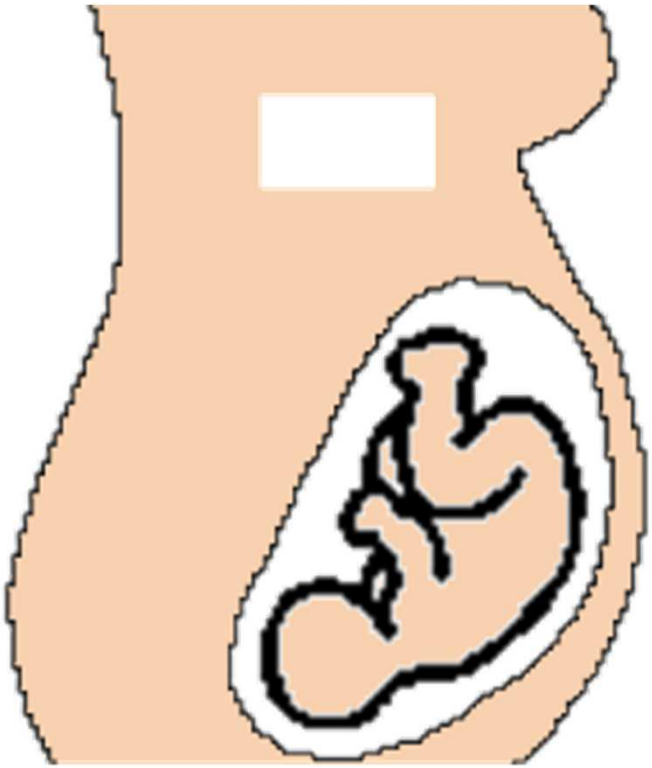
A new case of Maternal Phenylketonuria treated with Sapropterin Dihydrochloride (6R-BH4)

Journal:	*Gynecological Endocrinology*
Manuscript ID:	DGYE-2014-0022.R1
Manuscript Type:	Case Report
Date Submitted by the Author:	n/a
Complete List of Authors:	Aldámiz-Echevarría, Luis; Cruces University Hospital, Couce, Mª Luz; Clinic University Hospital of Santiago de Compostela, Llarena, Marta; Cruces University Hospital, Andrade, Fernando; Cruces University Hospital,

Homocisteína: factor de riesgo de complicaciones obstétricas

- Formación del feto: defectos tubo neural
- Complicaciones del embarazo que impliquen la vascularización de la placenta:
  - Preeclampsia
  - Abortos espontaneos y recurrentes
  - Abruptio placentae



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¿Podemos cambiar la historia natural mediante nuevas terapias?

Enfermedades lisosomales

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¿Son enfermedades del adulto?

Enfermedad de Fabry

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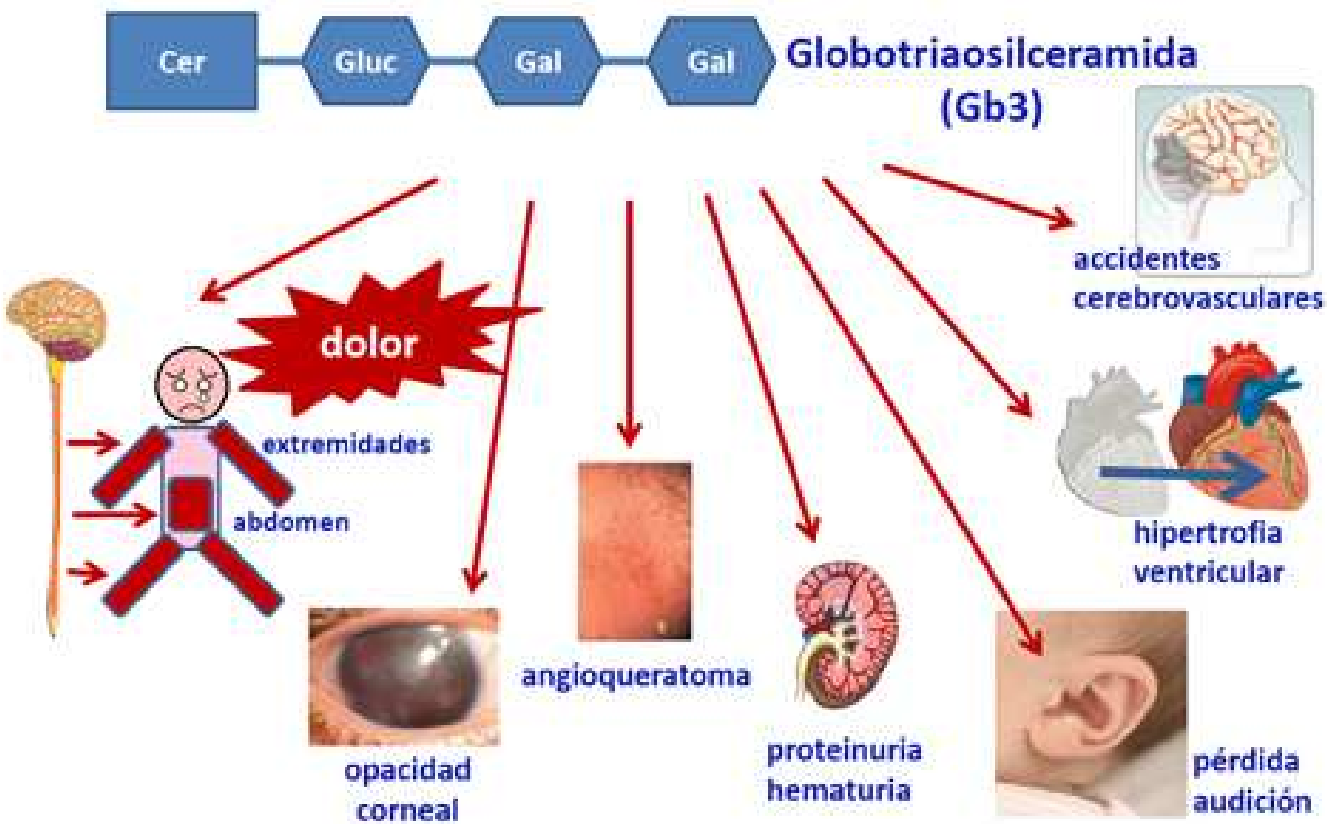
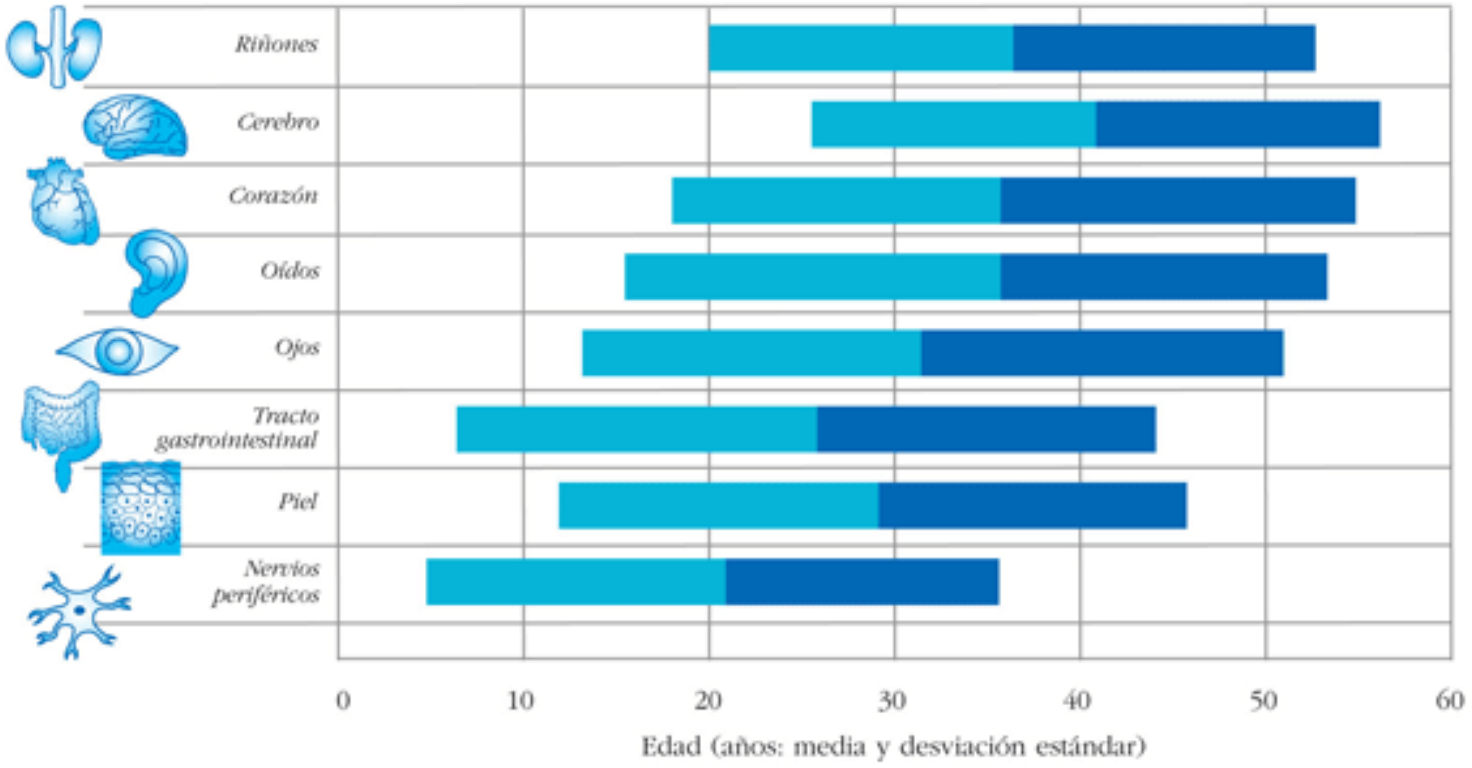
Manifestaciones clínicas de la enf. Fabry



Cronología de la enfermedad



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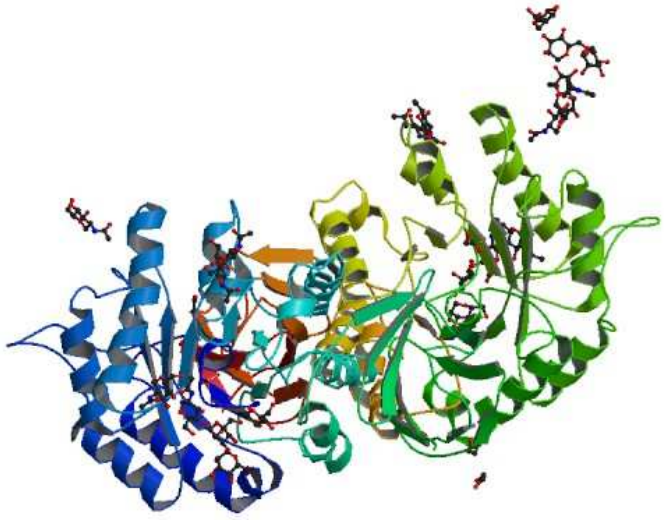
Enfermedad Fabry

- El deposito de Gb3 se inicia en el periodo fetal
- El estudio de la función renal, y de la microalbuminuria no detecta de modo precoz la lesión en el riñón
- El Gb3 y lysoGb3 no establecen el pronostico



α- galactosidasa A

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¿Podemos cambiar la historia natural mediante próximas nuevas terapias?

Enfermedades lisosomales

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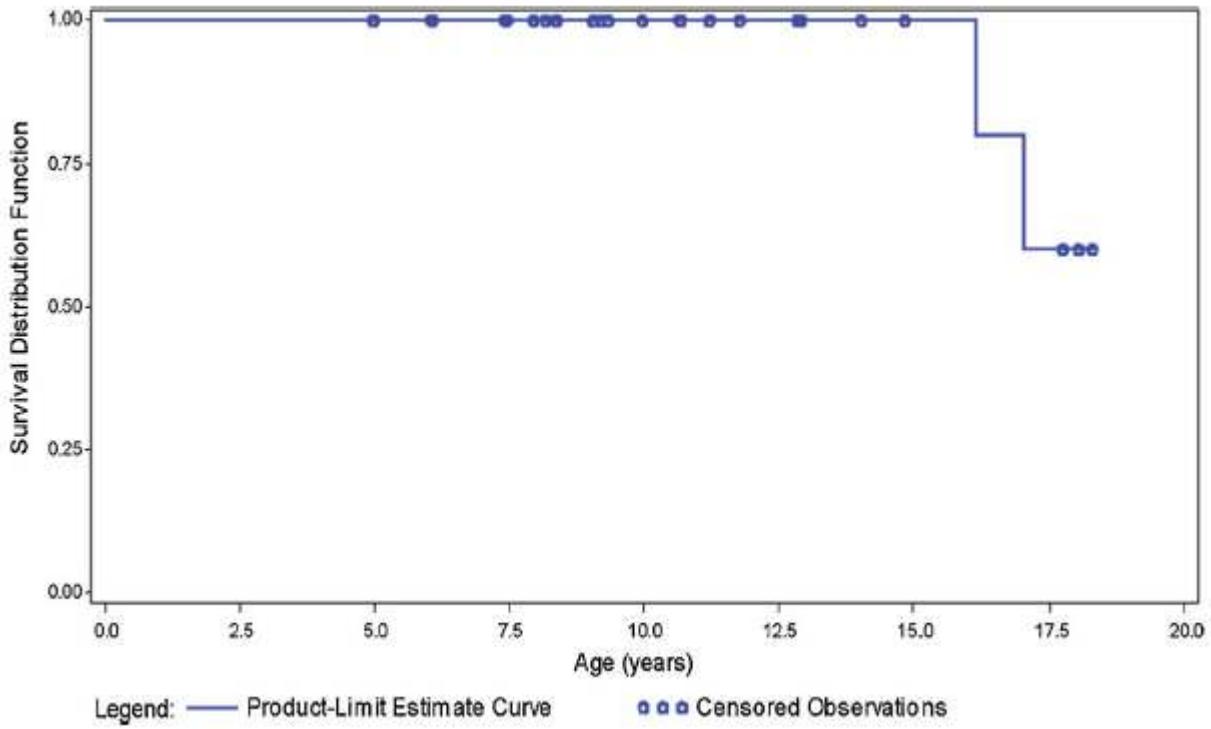
J Inherit Metab Dis (2014) 37:431–437
DOI 10.1007/s10545-013-9661-8

ORIGINAL ARTICLE

Natural history of Sanfilippo syndrome type A

Dakota Buhrman · Kavita Thakkar · Michele Poe · Maria L. Escolar



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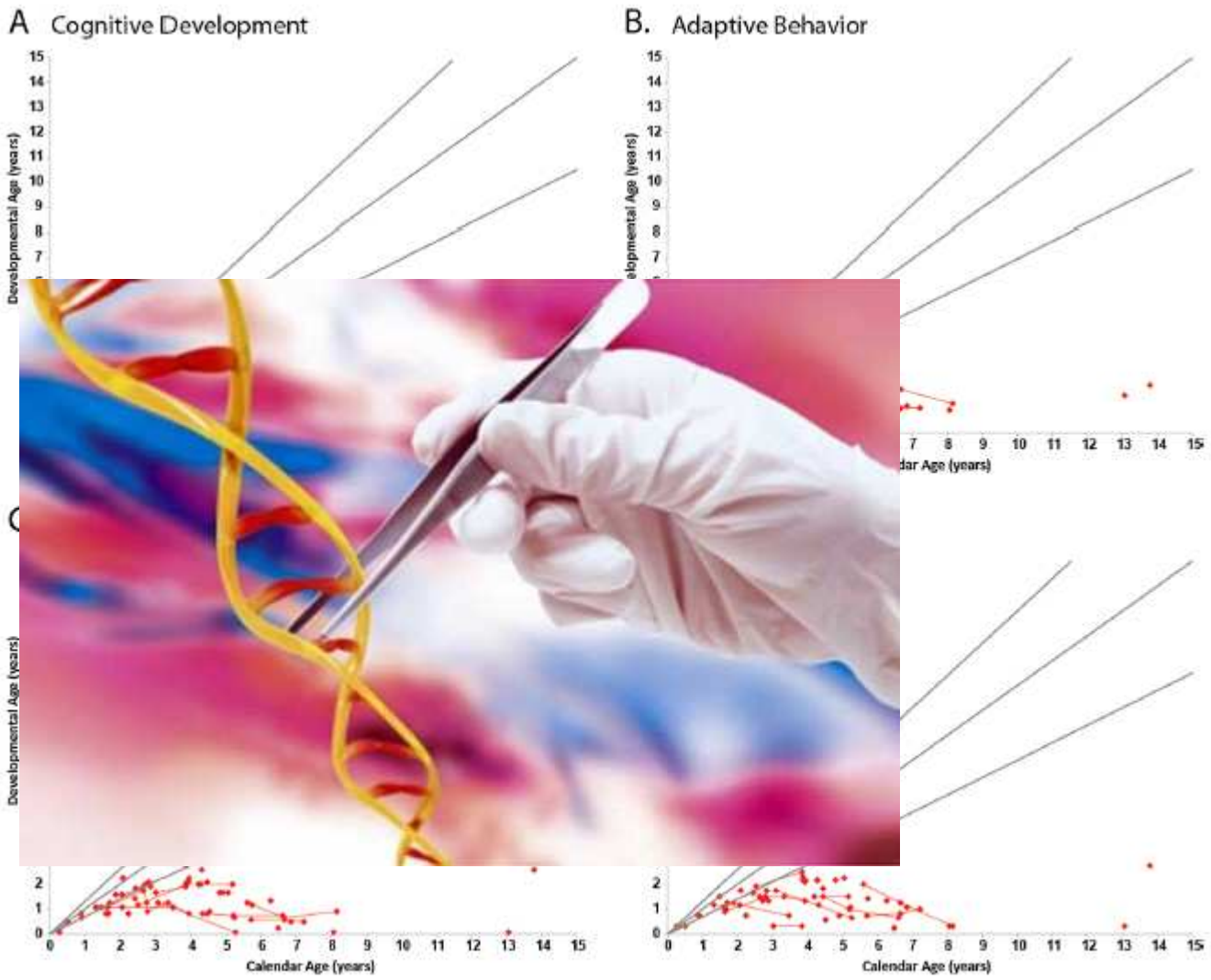

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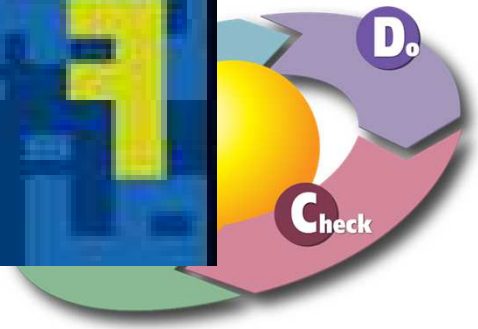
- En los EIM … storia natural
- El cribado … l
- Para una a … suficiente seguir un …
- Es el área … nismo en medicina



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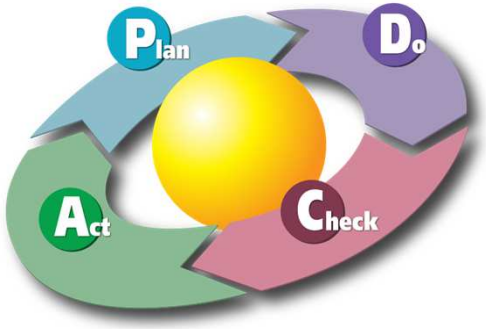
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Clinical Biochemistry 43 (2010) 411–415

Contents lists available at ScienceDirect

Clinical Biochemistry

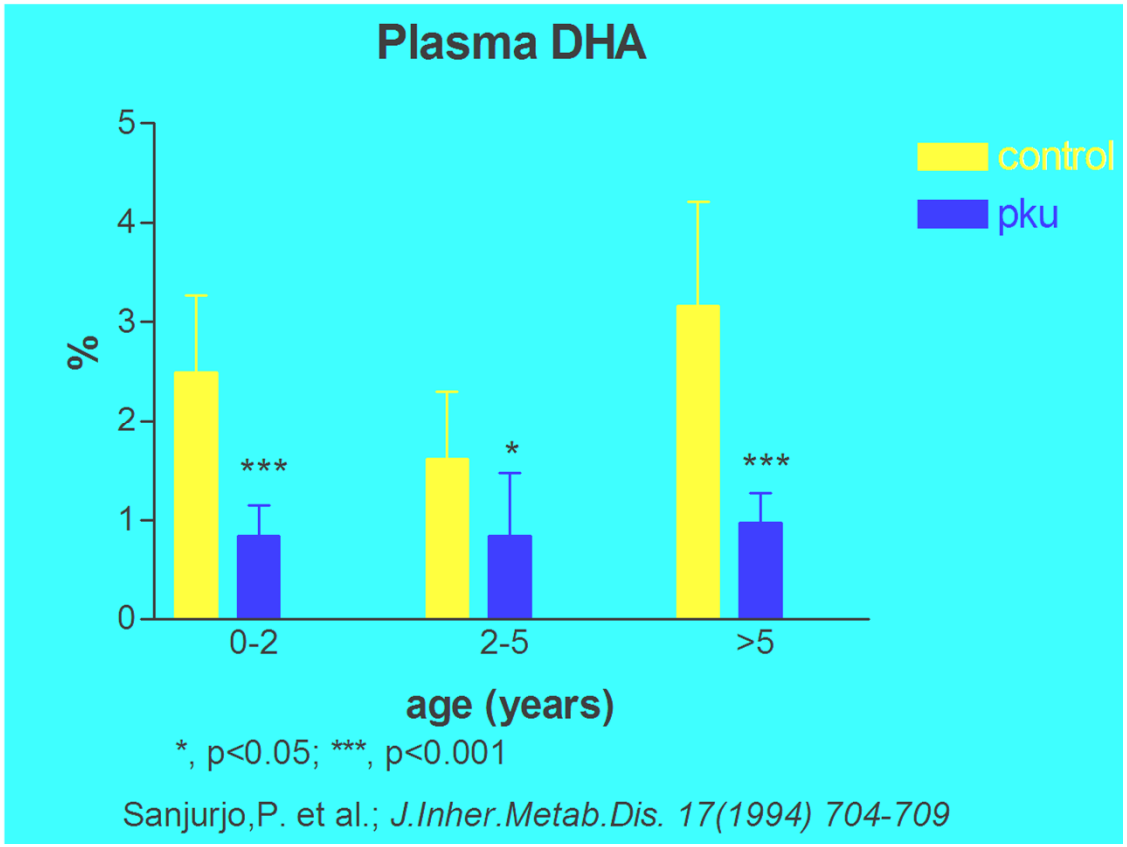
journal homepage: www.elsevier.com/locate/clinbiochem

Long-chain polyunsaturated fatty acid status in phenylketonuric patients treated with tetrahydrobiopterin

Maria A. Vilaseca [a,d,*], Nilo Lambruschini [b,d], Lilianne Gómez-López [b,d,e], Alejandra Gutiérrez [b,d], Juan Moreno [a], Mireia Tondo [a], Rafael Artuch [a,d,e], Jaume Campistol [c,d,e]

[a] Department of Biochemistry, Barcelona, Spain
[b] Division of Pediatric Gastroenterology, Hepatology and Nutrition, Barcelona, Spain
[c] Department of Neurology, Barcelona, Spain
[d] PKU follow-up Unit, Hospital Sant Joan de Déu, University of Barcelona, Spain
[e] Centre for Biomedical Research on Rare Diseases (CIBERER), Institute of Health Carlos III, Spain

PKU y ácidos grasos



Acidemia Glutarica tipo I
McKusick 231670

- Fue descripta por Goodman S en 1975 (*)
- Déficit de la enzima glutaril CoA dehidrogenasa (GCDH, EC 1.3.99.7),
- Herencia mendeliana simple autosómica recesiva
- Prevalencia general 1:100.000 – 30.000 (**)

(*) Goodman SI. Biochem Med 1975; 12: 12-21.

(**) Linder M. J Inherit Metab Dis 2004; 27: 851-859.

TABLE 1: Effect of Therapy-Related and -Unrelated Parameters on the Onset of MD in 52 Patients with GA-I Detected by NBS

Parameter	Patients, No.	Patients with MD, No. (mild/severe)	OR (95% CI)
Treatment[a]			
Full treatment	37	2 (2/0)	35.0 (5.88–208.39)
No full treatment	15	10 (4/6)	
Basic treatment[a]			
Full treatment	37	2 (2/0)	14.0 (2.01–97.31)
No basic treatment	9	4 (4/0)	
Emergency treatment[a]			
Full treatment	37	2 (2/0)	184.6 (7.92–4305.2)[b]
No emergency treatment	6	6 (0/6)	
Metabolic center			
Yes	45	8 (5/3)	6.17 (1.15–33.11)
No	7	4 (1/3)	
Metabolic center × treatment[a]			
MC = no, T = yes	2	1 (1/0)	34.0 (1.12–1030.42)
MC = yes, T = yes	35	1 (1/0)	
MC = no, T = no	5	3 (0/3)	0.64 (0.07–6.06)
MC = yes, T = no	10	7 (4/3)	
Migration background			
Yes	26	6 (2/4)	1.0 (0.36–4.01)
No	26	6 (4/2)	
Excretor status			
High excretor	39	10 (5/5)	1.90 (0.36–10.07)
Low excretor	13	2 (1/1)	

Similar results were obtained for the outcome parameters "acute encephalopathic crisis" (Supplementary Table 3) and "morbidity score" (Supplementary Table 4).
[a]In agreement with current treatment recommendations.[13]
[b]+0.5 was added to these cells to avoid division by zero.[21]
MD = movement disorder; GA-I = glutaric aciduria type I; NBS = newborn screening; OR = odds ratio; CI = confidence interval; MC = metabolic center; T = treatment according to the guideline.

CUIDADOS DE LA EMBARAZADA CON HIPERFENILALANINEMIA

- Prevención y diagnóstico de la embriopatía por PKU
- Programación del embarazo
- Tratamiento dietético
- Tratamiento farmacológico. Suplementos de vitaminas y minerales
- Cifras de Phe y de Tyr en el embarazo
- Controles

Homocistinuria: déficit de CBS

SNC

- Retraso mental
- Síndromes psiquiátricos
- Convulsiones
- S extrapiramidales

Ocular

- Ectopia lentis
- Miopia
- Glaucoma
- Cataratas
- Atrofia óptica

Oseo

- Osteoporosis
- Huesos marfanoide
- Escoliosis
- Aracnodactilia
- Genu valgum
- Vértebras bicóncavas
- Pies cavus

Vascular

- Oclusiones
- Flujo malar

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Homocisteína y folato en el embarazo

- La suplementación periconcepcional adecuada con folato en el periodo crítico de formación de órganos se asocia a una reducción del riesgo de anomalías congénitas, especialmente defectos del tubo neural

- La posible acción del folato en relación con los DTN radica en su implicación en el metabolismo de la homocisteína