ОПИСАНИЕ НА ПРЕДЛОЖЕНИЕТО ЗА ЗАБОЛЯВАНЕ
в съответствие с чл. 11, ал. 2 от Наредба № 16 от 30.07.2014 г. за условията и реда за регистриране на редките заболявания и за експертните центрове и референтните мрежи за редки заболявания. Издадена от Министъра на здравеопазването, обн., ДВ, бр. 67 от 12.08.2014 г.

ИНФОРМАЦИЯ ЗА:
Наименование на заболяването
Е 70.0 Класическа фенилкетонурия
Определение на заболяването
Хиперфенилаланинемията (ХФА) е хронично, абнормно увеличение на нивата на фенилаланин в кръвта. ХФА обикновено се проявява като следствие на два типа вродени дефекти на обмяната: фенилкетонурия и ВН4-дефицити. ФКУ е наследствено метаболитно заболяване, причинено от генетична мутация, водеща до дефицит на ензима фенилаланинхидроксилаза, нужен за метаболизирането на фенилаланина до тирозин. При липса на достатъчни количества от ензима или недостатъчното му функциониране, нивата на ФА се повишават в кръвта и мозъка, което води до умствено изоставане, гърчове, тремор и др.
Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)
Е 70.0
Код на заболяването по Orpha code
Епидемиологични данни за заболяването в Република България
В България честотата на класическата ФКУ е около 1:21 000, като е налице сравнително висока честота на леките ХФА и съотношение ФКУ/ХФА = 1:2.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
L Kalaydjieva, B Dworniczak, C Aulehla-Scholz, I Kremensky, J Bronzova, A Eigel, J Horst] Classical phenylketonuria in Bulgaria: RFLP haplotypes and frequency of the major mutatons JMed Genet 1990; 27: 742-745
Епидемиологични данни за заболяването в Европейския съюз
ФКУ е по-честа сред индивиди от кавказката или източноазиатската популации, където са около 1:10 000 – 15 0000 новородени . Въпреки това случаите на ФКУ не са разпределени равномерно: например постоянна ХФА се открива при 1 от 4 000 новородени в Турция и Северна Ирландия . Честотата в Латинска Америка варира от 1:25 000 до 1:50 000 новородени с по-ниска честота в северните части. Испания се различава от останалите европейски страни по това, че има сравнително висока честота на случаи с леко повишени нива на ФА, дължащи се на частична инактивация на РАН.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Mojca Zerjav Tansek, Urh Groselj, Natalija Angelkova, Dana Anton, Ivo Baric, Maja Djordjevic, Lindita Grimci, Maria Ivanova, Adil Kadam, Vjosa Kotori, Hajrija Maksic, Oana

Marginean, Otilia Margineanu, Olivera Miljanovic, Florentina Moldovanu, Mariana Muresan, Michaela Nanu, Mira Samardzic, Vladimir Sarnavka, Aleksei Savov, Maja Stojiljkovic, Biljana Suzic, Radka Tincheva, Husref Tahirovic, Alma Toromanovic, Natalia Usurelu and Tadej Battelino; Phenylketonuria screening and management in southeastern Europe – survey results from 11 countries; Orphanet Journal of Rare Diseases (2015) 10:68

2. Urh Groselj, Mojca Zerjav Tansek, Andraz Smon, Natalija Angelkova, Dana Anton, Ivo Baric, Maja Djordjevic, Lindita Grimci, Maria Ivanova, Adil Kadam, Vjosa Mulliqi Kotori, Hajrija Maksic, Oana Marginean, Otilia Margineanu, Olivera Milijanovic, Florentina Moldovanu, Mariana Muresan, Simona Murko, Michaela Nanu, Barbka Repic Lampret, Mira Samardzic, Vladimir Sarnavka,Aleksei Savov, Maja Stojiljkovic, Biljana Suzic, Radka Tincheva, Husref Tahirovic, Alma Toromanovic,
Natalia Usurelu, Tadej Battelino; Newborn screening in southeastern Europe; Molecular Genetics and Metabolism 113 (2014) 42–45

Оценка на съответствието на заболяването с дефиницията за рядко заболяване съгласно § 1, т. 42 от допълнителните разпоредби на Закона за здравето

Класическата фенилкетонурия е в съответствие с дефиницията за рядко заболяване съгласно §1, т. 42 от допълнителните разпоредби на Закона за здравеопазването и е под 1:100 000 души за България.

Критерии за диагностициране на заболяването

Откриването на биохимичните, а впоследствие и на молекулярно-генетичните причини за ФКУ, както и установяването на безспорния ефект от ФА-рестриктивната диета, води до необходимостта от ранно поставяне на диагнозата и осигуряване на максимално добър краен ефект за пациентите. Бързият прогрес на заболяването и бързото повлияване от диетата в ранна детска възраст, поставя за цел диагностицирането на заболяването да става в периода на новороденото.

Тест на Guthrie

Основата за развитието на неонаталните скринингови програми е поставена преди повече от 50 години от *Robert Guthrie* и неговия тест за бактериално инхибиране. Той започва разработването на теста през 1960г. и публикува детайлна методология през 1963г. Тестът се основава на капилярна кръв (взета от петата на детето) взета върху филтърна бланка и оставена да съхне при стайна температура. Дискове от напоената с кръв бланка се поставят върху агар, на който е култивиран *Bacillus subtilis* - микроорганизъм, нуждаещ се от фенилаланин за своя растеж. Гелът съдържа и β-2-тиенилаланин, който потиска растежа чрез инхибиране употребата на фенилаланин

Флуоресцентни методи

Най-чувствителен от тази група методи е нинхидриновият флуоресцентен метод, модификация на McCaman and Robins *1962.* Това е и основният метод използван за неонатален скрининг в България

Тандем мас спектрометричен метод (ТМС)

Тандем мас спектрометрията е разработена като надежден количествен метод за определяне концентрациите на аминокиселини в малки обеми кръв или плазма. Методът предоставя по-нисък процент на фалшиво положителни проби в сравнение с флуориметричния, където те достигат почти до 1%. Освен това позволява едновременното измерване на нивата на ФА и тирозин, както и определянето на

съотношението между тях.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1.Тинчева Р., А. Кадъм, Д. Авджиева, Фенилкетонурия – диагноза и лечение. Педиатрия 2014, 2, 57-60
2. Urh Groselj, Mojca Zerjav Tansek, Andraz Smon, Natalija Angelkova, Dana Anton, Ivo Baric, Maja Djordjevic, Lindita Grimci, Maria Ivanova, Adil Kadam, Vjosa Mulliqi Kotori, Hajrija Maksic, Oana Marginean, Otilia Margineanu, Olivera Milijanovic, Florentina Moldovanu, Mariana Muresan, Simona Murko, Michaela Nanu, Barbka Repic Lampret, Mira Samardzic, Vladimir Sarnavka,Aleksei Savov, Maja Stojiljkovic, Biljana Suzic, Radka Tincheva, Husref Tahirovic, Alma Toromanovic, Natalia Usurelu, Tadej Battelino; Newborn screening in southeastern Europe; Molecular Genetics and Metabolism 113 (2014) 42–45
3. Mojca Zerjav Tansek, Urh Groselj, Natalija Angelkova, Dana Anton, Ivo Baric, Maja Djordjevic, Lindita Grimci, Maria Ivanova, Adil Kadam, Vjosa Kotori, Hajrija Maksic, Oana Marginean, Otilia Margineanu, Olivera Miljanovic, Florentina Moldovanu, Mariana Muresan, Michaela Nanu, Mira Samardzic, Vladimir Sarnavka, Aleksei Savov, Maja Stojiljkovic, Biljana Suzic, Radka Tincheva, Husref Tahirovic, Alma Toromanovic, Natalia Usurelu and Tadej Battelino; Phenylketonuria screening and management in southeastern Europe – survey results from 11 countries; Orphanet Journal of Rare Diseases (2015) 10:68
4. Kathom, H., Avdjieva-Tzavella, D., Andonova, S., Takov, K., Tincheva, R., Savov, A.; Molecular epidemiology, genotype-phenotype correlation and BH4 responsiveness in phenylketonuria patients from Bulgaria - 2014, постер
Алгоритми за лечение на заболяването
Ранното и адекватно лечение осигурява нормално физическо, неврологично и когнитивно развитие на детето с фенилкетонурия. **А. Диетолечение** Основното лечение на фенилкетонурията е диета бедна на фенилаланин. Диетичната рестрикция трябва да започне максимално рано и да продължи стриктно по време на детството. Становището за продължителността на диетата претърпя много корекции, като сега е ясно, че има пациенти, при които тя трябва да бъде прилагана в същите рамки както при децата и след навършване на 18 год.възраст. Неврологичната симптоматика), когнитивните и/или поведенчески нарушения и промените в мозъчната ЯМР- находка при възрастни, прекъснали диетата, е в основата на консенсусно мнение, че специфичната ФКУ-диета трябва да се продължи цял живот. Периодите на най-рестриктивна диета са в детството, преконцепционно и по време на бременност. Диетата трябва да бъде съобразена с възрастта и теглото на пациента. Освен осигуряване на дневните нужди от фенилаланин, необходимо е да се достави оптимално количество протеин, микро- и макроелементи. Диетата при фенилкетонурия има три основни компонента: Синтетични протеини Обменни протеинови /белтъчни/ единици Безпротеинови /безбелтъчни/ храни ***1. Синтетични протеини*** Това са протеинови смеси без наличието на фенилаланин. Тези смеси са необходими, за да се посрещнат белтъчните нужди на организма и трябва да бъдат разпределени в дневния режим, така че да бъдат достигнати оптималните протеинови нива. Тези смеси съдържат и аминокиселината тирозин, която при пациенти с

фенилкетонурия не може да бъде произведена от организма, а е от основно значение за мозъка. Обогатени са с необходимите витамини и минерали.

2. Обменни протеинови единици

С тези единици се измерва количеството внесен в организма белтък, с който да се покриват дневните нужди от фенилаланин. Една обменна единица е количеството съдържащо 50 mg фенилаланин или около 1 g протеин (въпреки че растителните и животинските белтъци съдържат различно количество фенилаланин, се приема максималната стойност от 50 мг). Храните, които трябва да бъдат изчислявани в обменни единици са всички белтък съдържащи храни, което включва зърнени храни, картофи, варива и т.н. Броят на разрешените обменни единици варира според възрастта и индивидуалния толеранс и се определя от кръвните нива на фенилаланин. В кърмаческия период дневните нужди от фенилаланин се покриват от майчината кърма или от стандартни адаптирани млека.

3. Безбелтъчни храни

Това са храни, които не съдържат белтъци, но са богати на въглехидрати и мазнини. Те могат да бъдат консумирани свободно, за да се покриват енергийните нужди на организма, както и да се осигури разнообразието на хранителния режим, като се взима предвид калорийната необходимост.

Проследяването нивата на ФА при пациентите с ФКУ според Британските препоръки трябва да се провежда ежеседмично до 4г. възраст, на 2 седмици при деца на възраст 4-10 г., а след тази възраст веднъж месечно. Според европейските препоръки нивата на ФА се контролират веднъж седмично поне до 2 г. възраст, а след това поне веднъж месечно. Всяка година се определя костната възраст и евентуалното наличие на остеопороза (поради възможен белтъчен дефицит), на шестмесечие (при нужда и по-често) се следят психологично развитие, функционални чернодробни проби, пълна кръвна картина и ЕЕГ, мастен и глюкозен профил, поради превалиращите въглехидрати и мазнини, ако диетата не е правилно балансирана. При спазването на всички стандарти за диетолечение, децата с ФКУ не са по-често боледуващи от връстниците си, имат нормално пубертетно развитие. При боледуване, ваксиниране, гладуване, никнене на зъби и други стресови ситуации, се очакват повишения в нивата на ФА, които са краткотрайни и без екстремни пикове, като се предполага, че те не влияят на прогнозата на развитие. Важно е да не се допуска внасянето на фенилаланина за денонощието само с едно или две хранения, а да се разпредели максимално равномерно, тъй като големите денонощни флуктуации се свързват с намалени IQ-нива, макар и в неголяма степен.

Б. Лечение с тетрахидробиоптерин (BH_4)

Освен диетолечението, съществува и медикаментозно лечение, което е свързано с дефицитите на тетрахидробиоптерин. Сапоптерин хидрохлорид е синтетична форма на тетрахидробиоптерин, кофактор на ензима ФАХ. Неговото приложение за лечение на ФКУ се базира на хипотезата, че при определени мутации, приложението му води до повишаване на ензимната активност. В групата на пациенти с фенилкетонурия има такива, по литературни данни около 30% , които са"респондери" на такъв тип лечение. Прилага се перорално. Тестът с BH_4 се налага, като един от най-евтините и леснодостъпни за подобна диагностика. Първоначално тестът с натоварване с BH_4 е използван за разграничаване между пациентите с ФКУ и тетрахидробиоптеринов дефицит. Този тест е лесно приложим поради това, че макар птерините да се измерват

само в някои центрове, измерването на нивата на фенилаланин и тирозин е достъпно на много места.

В. Ензимзаместителна терапия

За съжаление пациентите с тежки форми на класическа ФКУ, както и някои не-ФКУ хиперфенилаланинемии, не отговарят на лечение с BH_4, поради липса на остатъчна ФАХ-активност, която да бъде стимулирана с кофактора. Подобни нереспондери са показани за ЕЗТ, която за разлика от отговора към BH_4, не зависи от генотипа. Въпреки че парциалната чернодробна трансплантация би могла да разреши проблема с производството на ензим, рисковете от оперативната интервенция и доживотната имуносупресивна терапия водят до отхвърлянето й като метод на лечение. Ензимзаместващата терапия при фенилкетонурията може да бъде проведена чрез внасяне на рекомбинантен ензим фенилаланинхидроксилаза. За разлика от провежданото при лизозомните болести ензимзаместващо лечение тук проблемите са повече - от една страна ензимът е нестабилен, от друга страна за да действа адекватно той има нужда от интактен мултиензимен комплекс, участващ в разграждането на фенилаланина. В експериментален етап е терапия, при която ензимът фенилаланинхидроксилаза се замества от фенилаланин амонилиаза, кофактор-независим растителен протеин, който води до леки и краткотрайни намаления на ФА-нива.

Г. Прием на дълговерижни неутрални аминокиселини

Дълговерижните неутрални аминокиселини имат обща транспортна система с фенилаланина за навлизане в ЦНС. Счита се, че конкурирането за транспортния протеин води до намаляване на мозъчните ФА-концентрации(24). Приемът на дълговерижни неутрални аминокиселини има няколко цели: да намали абсорбцията на фенилаланин в гастроинтестиналния тракт, което да доведе до намаляване количеството на фенилаланина в плазмата и от там в мозъка, да повиши концентрацията на невротрансмисери и есенциални аминокиселини в мозъка. Освен това повишеният прием на тирозин и триптофан, води до по-бърза регенерация на BH_4. Лечението с дълговерижни неутрални аминокиселини се приема от някои автори като алтернатива на диетичното лечение при фенилкетонурията, но по-често се прилага в комбинация с него.

Д. Приложение на фармакологични чаперони

Голяма част от наследствените метаболитни болести са резултат от синтез на нестабилни клетъчни протеини. В зависимост от причината, довела до това нарушение тези заболявания могат да бъдат разделени на две групи:

- Токсично нарушение на клетъчната функция поради синтез на мутантен белтък с нарушено разграждане, което води до натрупване на амилоид
- Нарушение на клетъчната функция, но мутантния, нестабилен протеин може да бъде разграден

Новият терапевтичен подход за лечение на този тип наследствени болести е използване на фармакологични чаперони.- малки молекули, които водят до стабилизиране на прицелния протеин. Прилагат се и при двата типа нарушение на клетъчната функция. При ФКУ са установени над 500 патологични мутации, една част от които водят до синтез на нестабилна ФАХ. Има обещаващи резултати от експерименталното приложение на това лечение за стабилизиране активността на ФАХ при определени мутации.

Е. Генна терапия

До момента съществуват множество успешни опити за генна терапия при мишки с ФКУ

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Blau N, Burgard P. Disorders of Phenylalanine and Tetrahydrobiopterin Metabolism. In: Blau N, Leonard J, Hoffmann G, Clarke J, editors. Physician's Guide to the Treatment and Follow-up of Metabolic Diseases. Heidelberg: Springer; 2006. p. 25-34.
2. Camp K., Michele A. Lloyd-Puryear, and Kathleen L. Huntington
Nutritional Treatment for Inborn Errors of Metabolism: Indications, Regulations, and Availability of Medical Foods and Dietary Supplements Using Phenylketonuria as an Example
Mol Genet Metab. 2012 September ; 107(1-2): 3–9.

Алгоритми за проследяване на заболяването

Показатели и изследвания	**изх.**	**6 м.**	**+ 12 м.***	**+ 24 м.***
Телесна меса	x	x	x	x
Ръст	x	x	x	x
Обиколка на глава	x	x	x	x
ПКК (хемоглобин, хематокрит, еритроцити, левкоцити, тромбоцити)	x	x	x	x
ASAT	x	x	x	x
ALAT	x	x	x	x
Фенилаланин и аминокиселини в плазма	x		x	x
Абдоминална ехография-размери на черен дроб и слезка	x	x	x	x
ЕЕГ	x		x	x

Педиатрия 2014, 2, 57-60
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Необходими дейности за профилактика на заболяването (ако такива са приложими)
Всяко семейството получава подходяща генетична консултация, както и ще получи подходящо медицинско проследяване. Пренатална диагноза на класическата фенилкетонурия може да се прави в култура амниоцити или проби хорионни въси.
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Фенилкетонурия - диагноза и лечение

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Ключови думи: *фенилкетонурия, фенилаланинхидроксилаза, диетолечение, тетрахидробиоптерин (BH4), Guthrie-тест, фенилаланин амонилиаза, дълговерижни неутрални аминокиселини, Куван*

Фенилкетонурията (ФКУ) и хиперфенилаланинемията (ХФ) са наследствени метаболитни болести, резултат от дефицит на ензима фенилаланинхидроксилаза (ФАХ), участващ в метаболизирането на фенилаланина (ФА) до L-тирозин. Описана е за първи път от норвежкия лекар Фьолинг (Ivar Asbjurn Fulling) през 1934 год. при две деца от едно семейство с изоставане в нервно- психическото развитие, чиято урина била със специфична миризма. Опитвайки се да установи връзка между психическото изоставане и миризмата, той изследва урината на голяма група деца със същата симптоматика за редица вещества, включително кетони. Установявайки фамилност в наблюдаваните случаи той предполага, че се касае за автозомно рецесивно метаболитно заболяване. В края на 50-те години на миналия век е създаден първия тест за диагностика на фенилкетонурията от Robert Guthrie, с което се поставя началото на скрининг за това заболяване при новородени през 60-те и 70-те години(5). В България масов неонатален скрининг за диагностика на ФКУ е започнат през 1978 год. Проучванията през 80-те и 90-те водят до локализиране на гена на ФАХ върху 12-та хромозома, а впоследствие идентифицирането на повече от 500 мутации в този ген (13,15).

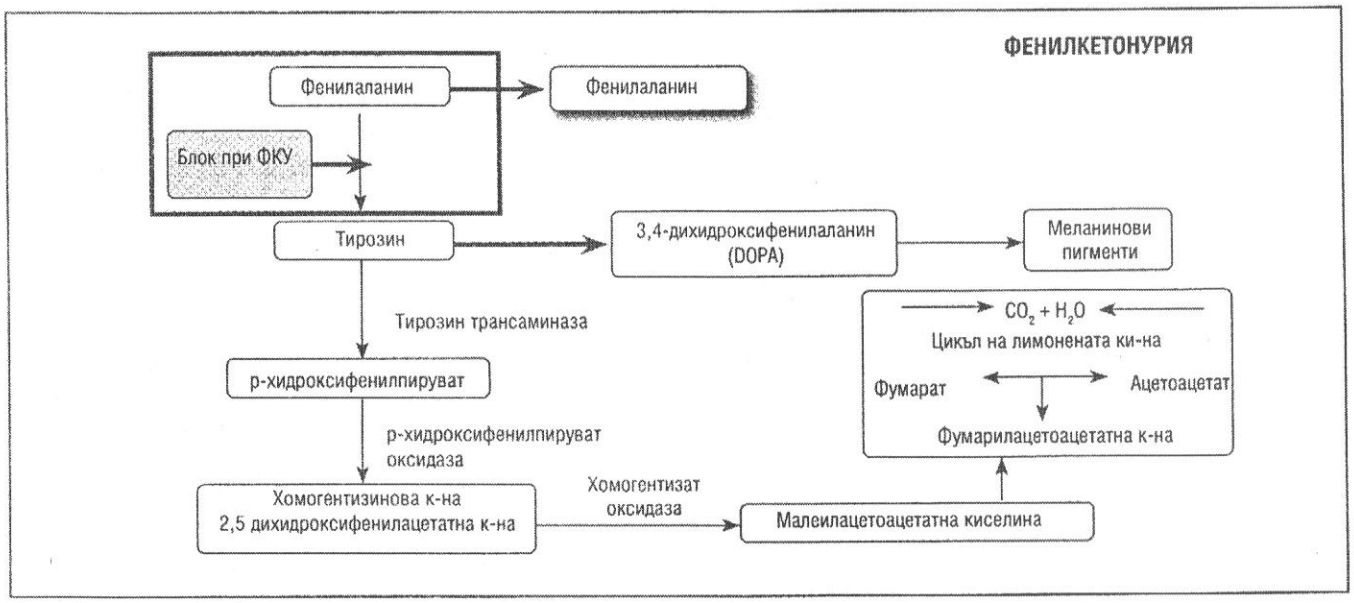
През 1951, немският професор Horst Bickel разработва първото, несъдържащо фенилаланин мляко за тези пациенти. Фенилкетонурията е първото заболяване, при което диетичното лечение води до нормално физическо и психическо развитие на детето, ако е започнато рано след неговото раждане.

ЕТИОЛОГИЯ

Фенилаланина е есенциална аминокиселина, необходима за белтъчната обмяна в човешкия организъм. Неговото ниво се поддържа постоянно чрез добре регулирана динамична система на внос и разграждане. Разграждането на ФА до тирозин става в хидролизираща система, състояща се от ензима ФАХ, неконюгирания птерин кофактор тетрахидробиоптерин (BH4) и ензимите дихидроптеридин редуктаза и 4 α-карбиноламин дехидратаза, които участват във възстановяването на BH4 (1).

Фенилаланинхидроксилазата катализира превръщането на ФА в тирозин и представлява скоростоопределящ етап в единствения клинично значим биохимичен път за катаболизма на фенилаланина (22). Тъй като това е пътя, по който се синтезира тирозинът, то при фенилкетонурия последният се превръща в есенциална аминокиселина. Метаболизмът на фенилаланина в норма и при фенилкетонурия е представен на ***фиг. 1.***

Основната активност на ФАХ е в черния дроб. За активирането на ензима е необходимо свързване на трите субстрата - фенилаланин, молекулен кислород и кофактор BH4 (25). Високите нива на фенилаланин водят до пренасочването му към трансаминазна реакция с глутамат, при която се получават фенилацетат, фенилпируват и фенетиламин (10). Повишените нива на тези метаболити, заедно с преминаването на фенилаланина през хемато-енцефалната бариера, са основна причина за умственото изоставане при ФКУ.



Фиг.1 Метаболизъм на фенилаланина

Точните механизми, по които се увреждa мозъка, все още не са напълно известни, но невропатологичните промени при лекувани и нелекувани пациенти показват нарушения в миелинизацията (9). Фактори, участващи в невротоксичността на производните на фенилаланина са дефицита на тирозин и ролята на повишеното ниво на ФА за транспорта на други метаболити през кръвно-ликворната бариера.

ДИАГНОЗА

В България масовият неонатален скрининг се провежда на 3 - тия ден след раждането (12). Като гранична стойност се приема 240 µmol/L (3-4 mg/dL). Използваните методи са (1):

- Guthrie-тест, основан на растежа на бактериални колонии от Bacillus subtilis
- Флуориметричен метод
- Тандем масспектрометрия (TMS)

КЛАСИФИКАЦИЯ

Нивото на фенилаланин, изискващо терапевтична намеса е над 360 µmol/L (6 mg/dL). Пациенти с нива на фенилаланина (преди лечението) в рамките на 240-600 µmol/L (4-10 mg/dL) се класифицират като лека/преходна хиперфенилаланинемия; нива от 600 до 1200 µmol/L (10-20 mg/dL) се приемат за лека форма на фенилкетонурия; нива над 1200 µmol/L (20 mg/dL) се приемат за „класическа фенилкетонурия".

КЛИНИЧНА КАРТИНА

Фенилкетонурията е автозомно-рецесивно заболяване, което означава 25% риск за повторение при следваща бременност. В неонаталния период липсват специфични соматични промени при новороденото. Единствената находка може да бъде специфичната „миша миризма" на урината.

Симптомите при ФКУса свързани с два основни патофизиологични механизма - увреждане от натрупаните токсични продукти и увреждане от липсата на продукти от тирозиновата каскада - L-тироксин, меланин, допамин, катехоламини и др. (4).

Нелекуваните деца с класическа фенилкетонурия развиват част от симптомите след 6 месечна възраст: тежък интелектуален дефицит, микроцефалия, спастицитет, гърчове, атаксия, моторен дефицит, поведенчески промени, в част от случаите са съпътствани от прояви на аутизъм, автоагресия, импулсивност и психози. Степента на засягане зависи от възрастта на поставяне на диагнозата и началото на лечението, но увреждането на ЦНС е необратимо при късно започване на терапия.

Неонаталният скрининг дава възможност лечението на детето с фенилкетонурия да започне максимално рано, в рамките на първия месец след раждането. Адекватното лечение и проследяване на тези пациенти не винаги гарантира отсъствие на невропсихологическо засягане, като такива вариации в клиничните прояви на заболяването могат да се наблюдават и в рамките на едно семейство (18). Връзката между коефициента на интелигентност на детето и колебанията в нивата на фенилаланина е добре известна. Не е доказана корелация между изоставането в нервнопсихическото развитие и морфологични промени в ЦНС, установени чрез ЯМР (9).

ЛЕЧЕНИЕ

Ранното и адекватно лечение осигурява нормално физическо, неврологично и когнитивно развитие на детето с фенилкетонурия.

А. Диетолечение

Основното лечение на фенилкетонурията е диета бедна на фенилаланин. Диетичната рестрикция трябва да започне максимално рано и да продължи стриктно по време на детството (3). Становището за продължителността на диетата претърпя много корекции, като сега е ясно, че има пациенти, при които тя трябва да бъде прилагана в същите рамки както при децата и след навършване на 18 год. възраст. Неврологичната симптоматика), когнитивните и/или поведенчески нарушения и промените в мозъчната ЯМР-находка при възрастни, прекъснали диетата, е в основата на консенсусно мнение, че специфичната ФКУ-диета трябва да се продължи цял живот (8). Периодите на най-рестриктивна диета са в детството, преконцепционно и по време на бременност.

Диетата трябва да бъде съобразена с възрастта и теглото на пациента. Освен осигуряване на дневните нужди от фенилаланин, необходимо е да се достави оптимално количество протеин, микро- и макроелементи (11). В следващата таблица са представени основните параметри, които трябва да бъдат спазени при определянето на диетата при деца.

Възраст	ФА мг./24 ч.	Белтък, гр./24ч.
0-3 м.	130-400	2,1-2,3 гр./кг
4-12 м.	130-400	2,0-2,1 гр./кг
1 до 4 г.	200 - 400	≥ 30
4 до 7 г.	210 - 450	≥ 35
7 до 11 г.	220 - 500	≥ 40
11 до 14 г.	225-900	≥ 55
15 до 19 г.	295-1100	≥ 65
над 19 г.	290-1200	≥ 70

Диетата при фенилкетонурия има три основни компонента (6):

- Синтетични протеини
- Обменни протеинови /белтъчни/ единици
- Безпротеинови /безбелтъчни/ храни

1. Синтетични протеини

Това са протеинови смеси без наличието на фенилаланин. Тези смеси са необходими, за да се посрещнат белтъчните нужди на организма и трябва да бъдат разпределени в дневния режим, така че да бъдат достигнати оптималните протеинови нива. Тези смеси съдържат и аминокиселината тирозин, която при пациенти с фенилкетонурия не може да бъде произведена от организма, а е от основно значение за мозъка. Обогатени са с необходимите витамини и минерали.

2. Обменни протеинови единици

С тези единици се измерва количеството внесен в организма белтък, с който да се покриват дневните нужди от фенилаланин. Една обменна единица е количеството съдържащо 50 mg фенилаланин или около 1 g протеин (въпреки че растителните и животинските белтъци съдържат различно количество фенилаланин, се приема максималната стойност от 50 мг). Храните, които трябва да бъдат изчислявани в обменни единици са всички белтък съдържащи храни, което включва зърнени храни, картофи, варива и т.н. Броят на разрешените обменни единици варира според възрастта и индивидуалния толеранс и се определя от кръвните нива на фенилаланин. В кърмаческия период дневните нужди от фенилаланин се покриват от майчината кърма или от стандартни адаптирани млека.

3. Безбелтъчни храни

Това са храни, които не съдържат белтъчини, но са богати на въглехидрати и мазнини. Те могат да бъдат консумирани свободно, за да се покриват енергийните нужди на организма, както и да се осигури разнообразието на хранителния режим, като се взима предвид калорийната необходимост.

Проследяването нивата на ФА при пациентите с ФКУ според Британските препоръки трябва да се провежда ежеседмично до 4 г. възраст, на 2 седмици при деца на възраст 4-10 г., а след тази възраст веднъж месечно. Според европейските препоръки нивата на ФА се контролират веднъж седмично поне до 2 г. възраст, а след това поне веднъж месечно. Всяка година се определя костната възраст и евентуалното наличие на остеопороза (поради възможен белтъчен дефицит), на шестмесечие (при нужда и по-често) се следят психологично развитие, функционални чернодробни проби, пълна кръвна картина и ЕЕГ, мастен и глюкозен профил, поради превалиращите въглехидрати и мазнини, ако диетата не е правилно балансирана (18). При спазването на всички стандарти за диетолечение, децата с ФКУ не са по-често боледуващи от връстниците си, имат нормално пубертетно развитие. При боледуване, ваксиниране, гладуване, никнене на зъби и други стресови ситуации, се очакват повишения в нивата на ФА, които са краткотрайни и без екстремни пикове, като се предполага, че те не влияят на прогнозата на развитие. Важно е да не се допуска внасянето на фенилаланина за денонощието само с едно или две хранения, а да се разпредели максимално равномерно, тъй като големите денонощни флуктуации се свързват с намалени IQ-нива, макар и в неголяма степен.

Б. Лечение с тетрахидробиоптерин (BH4)

Освен диетолечението, съществува и медикаментозно лечение, което е свързано с дефицитите на тетрахидробиоптерин. Сапроптерин хидрохлорид е синтетична форма на тетрахидробиоптерин, кофактор на ензима ФАХ. (3) Неговото приложение за лечение на ФКУ се базира на хипотезата, че при определени мутации, приложението му води до повишаване на ензимната активност. В групата на пациенти с фенилкетонурия има такива, по литературни данни около 30%, които са „респондери" на такъв тип лечение (14,16). Прилага се перорално. Тестът с BH4 се налага, като един от най-евтините и леснодостъпни за подобна диагностика. Първоначално тестът с натоварване с BH4 е използван за разграничаване между пациентите с ФКУ и тетрахидробиоптеринов дефицит. Този тест е лесно приложим поради това, че макар птерините да се измерват само в някои центрове, измерването на нивата на фенилаланин и тирозин е достъпно на много места.

В. Ензимзаместителна терапия

За съжаление пациентите с тежки форми на класическа ФКУ, както и някои не-ФКУ хиперфенилаланинемии, не отговарят на лечение с BH4, поради липса на остатъчна ФАХ-активност, която да бъде стимулирана с кофактора. Подобни нереспондери са показани за ЕЗТ, която за разлика от отговора към BH4, не зависи от генотипа. Въпреки че парциалната чернодробна трансплантация би могла да разреши проблема с производството на ензим, рисковете от оперативната интервенция и доживотната имуносупресивна терапия водят до отхвърлянето ѝ като метод на лечение. Ензимзаместващата терапия при фенилкетонурията може да бъде проведена чрез внасяне на рекомбинантен ензим фенилаланинхидроксилаза. За разлика от провежданото при лизозомните болести ензимзаместващо лечение тук проблемите са повече - от една страна ензимът е нестабилен, от друга страна за да действа адекватно той има нужда от интактен мултиензимен комплекс, участващ в разграждането на фенилаланина (7). В експериментален етап е терапия, при която ензимът фенилаланинхидроксилаза се замества от фенилаланин амонилиаза, кофактор-независим растителен протеин, който води до леки и краткотрайни намаления на ФА-нива (20,21).

Г. Прием на дълговерижни неутрални аминокиселини

Дълговерижните неутрални аминокиселини имат обща транспортна система с фенилаланина за навлизане в ЦНС. Счита се, че конкурирането за транспортния протеин води до намаляване на мозъчните ФА-концентрации (24). Приемът на дълговерижни неутрални аминокиселини има няколко цели: да намали абсорбцията на фенилаланин в гастроинтестиналния тракт, което да доведе до намаляване количеството на фенилаланина в плазмата и от там в мозъка, да повиши концентрацията на невротрансмисери и есенциални аминокиселини в мозъка. Освен това повишеният прием на тирозин и триптофан, води до по-бърза регенерация на BH4. Лечението с дълговерижни неутрални аминокиселини се приема от някои автори като алтернатива на диетичното лечение при фенилкетонурията, но по-често се прилага в комбинация с него.

Д. Приложение на фармакологични чаперони

Голяма част от наследствените метаболитни болести са резултат от синтез на нестабилни клетъчни протеини (19). В зависимост от причината, довела до това нарушение тези заболявания могат да бъдат разделени на две групи (16):

- Токсично нарушение на клетъчната функция поради синтез на мутантен белтък с нарушено разграждане, което води до натрупване на амилоид
- Нарушение на клетъчната функция, но мутантния, нестабилен протеин може да бъде разграден

Новият терапевтичен подход за лечение на този тип наследствени болести е използване на фармако-

логични чаперони - малки молекули, които водят до стабилизиране на прицелния протеин. Прилагат се и при двата типа нарушение на клетъчната функция. При ФКУ са установени над 500 патологични мутации, една част от които водят до синтез на нестабилна ФАХ. Има обещаващи резултати от експерименталното приложение на това лечение за стабилизиране активността на ФАХ при определени мутации (23).

Е. Генна терапия

До момента съществуват множество успешни опити за генна терапия при мишки с ФКУ (11).

Майчин ФКУ - синдром

Високите нива на фенилаланин са тератогенни и са причина за повишен риск от спонтанни аборти. Фетусът страда от повишените ФА-нива, които водят до интраутеринно изоставане в растежа, лицев дисморфизъм, микроцефалия, вродени сърдечни аномалии, изоставане в развитието, гърчове и бъдещ интелектуален дефицит (2,17). Феталното излагане на високи концентрации фенилаланин зависи от трансплацентарния ФА-градиент: приблизително съотношение между феталните и майчините нива. Поради тези причини се изисква стриктна предконцепционна диета с таргетен интервал между 100 и 360 µmol/l при майки с ФКУ. Нивата на ФА подлежат на ежеседмичен контрол.

Пренатална диагностика

Пренатална диагностика е налична за всички форми на ФАХ и ВН4 дефицитите. За всички варианти метод на избор е определянето на мутациите.

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Classical phenylketonuria in Bulgaria: RFLP haplotypes and frequency of the major mutations.

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J Med Genet 1990 27: 742-745
doi: 10.1136/jmg.27.12.742

J Med Genet 1990; 27: 742–745

Classical phenylketonuria in Bulgaria: RFLP haplotypes and frequency of the major mutations

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Abstract

RFLP haplotypes and common mutations in the phenylalanine hydroxylase gene have been studied in a group of 29 Bulgarian PKU families. Haplotype distribution differs from that in other European populations, with a predominance of haplotypes 2 and 6 and a total absence of haplotype 3. The amino acid substitution in codon 408 is the most frequent molecular defect. The splicing defect in intron 12 is not found in Bulgarian PKU patients. Testing for three mutations, reported to be common among haplotype 1 and 4 alleles, has shown that they occur less frequently in Bulgarian PKU patients. Screening with five pairs of allele specific oligonucleotides failed to show the mutation in 59% of the patients. These findings add to the evidence that PKU is heterogeneous and that significant interpopulation differences exist. At present, DNA data cannot be used as an aid in early clinical classification and prognosis of hyperphenylalaninaemia in Bulgaria.

Neonatal screening in Bulgaria, with nearly one million neonates tested, has shown an incidence of classical phenylketonuria (PKU) of 1 in 21 000 and a relatively high frequency of mild hyperphenylalaninaemia (HPA) with a PKU/HPA ratio of 1/2. Experience has shown that both parental anxiety and non-compliance with the diet are frequent problems which require prompt classification of the phenylalaninaemias detected by the screening.

Studies of DNA polymorphisms in Danish HPA families established a correlation between the patients' phenotypes and their restriction fragment length polymorphism (RFLP) haplotypes.[1] This finding, and complementary studies of β thalassaemia,[2] suggested linkage between RFLP haplotypes and specific mutations in the phenylalanine hydroxylase (PAH) gene. The finding of a G to A transition at the splice donor site of intron 12 in haplotype 3 chromosomes,[3] and of an amino acid substitution in codon 408 of the PAH gene linked to haplotype 2,[4] gave credence to the above suggestions. These findings also indicated that PKU is genetically homogeneous and that the 'founder effect' played a major role in its spread. However, more recent data from other European populations showed a variable pattern of haplotypes and mutations and suggested that PKU is more heterogeneous than was initially thought.[5–7]

This work aimed to study the molecular basis of phenylketonuria in Bulgaria in comparison with other Caucasian populations and to evaluate the feasibility of using DNA data in early clinical classification and prognosis.

Materials and methods

PATIENTS

The study included 29 PKU patients and 50 heterozygous parents, that is, 58 mutant and 50 normal alleles. Eleven patients were of Turkish ethnic background. The patients were classified as having classical PKU using the criteria described by Güttler,[8] namely neonatal phenylalanine levels >1200 μmol/l, residual PAH activity below 1% (calculated from the protein loading data as described by Trefz *et al*[9]), and phenylalanine tolerance less than 20 mg/kg (data on tolerance are not yet complete in patients under 5 years of age). In cases detected late, high blood phenylalanine and the presence of severe mental retardation served as the main criteria.

METHODS

DNA was isolated from peripheral leucocytes as described previously.[10] For haplotype analysis, DNA samples were digested with *Bgl*II, *Pvu*II, *Eco*RI, MspI, *Xmn*I, *Hin*dIII, and *Eco*RV. Southern

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Received for publication 21 June 1990.
Accepted for publication 25 June 1990.

blot analysis was performed as described previously[11] using ^{32}P labelled cDNA probe phPAH 247.[12]

The samples were screened for the presence of the following mutations previously reported to occur in West European populations: exon 5, codon 158 (CGG→CAG)[13 14]; exon 7, codon 261 (CGA→CAA)[14]; exon 7, codon 281 (CCT→CTT)[15]; exon 12, codon 408 (CGG→TGG)[4]; exon 12, 5′ splice donor site (GT→AT).[3] The presence of each mutation was tested after amplification of exons 5, 7, and 12 and the flanking intronic sequences in the PAH gene. PCR conditions were as described previously.[16] Dot blot hybridisation with ^{32}P labelled allele specific oligonucleotides (ASO) was used to detect the presence of the mutations.[17] The sequences of the oligonucleotide probes were as described.[3 4 14 15] Previously studied patients of German origin,[5 12 15] whose genotypes had been confirmed by direct sequencing, served as positive and negative controls.

Results

RFLP HAPLOTYPES

Haplotype assignment was possible in 25 out of 29 families. The RFLP data are shown in table 1. Seven different RFLP haplotypes were found in the group of mutant alleles. Haplotype 2 was the most common and occurred in 38% of mutant alleles. Second in frequency was haplotype 6 (22%), which was found mainly in patients of Turkish origin. These two haplotypes were in linkage disequilibrium with the PKU gene ($\chi^2=14{\cdot}99$, $p<0{\cdot}001$ for haplotype 2 and $\chi^2=6{\cdot}11$, $p<0{\cdot}05$ for haplotype 6). Haplotypes 1 and 4 were also found to be relatively common and occurred in mutant chromosomes with frequencies similar to those seen in normal alleles. Haplotype 3 was absent altogether in the group studied. Eight out of 25 patients were haplotype homozygotes.

The polymorphic characteristics of normal chromosomes were heterogeneous, with a prevalence of haplotypes 1 (24%) and 4 (15%). In the 42 normal alleles where haplotype assignment was possible, a total of 20 different haplotypes was found, most of which occurred in single chromosomes.

Table 1 Percentage distribution of RFLP haplotypes in PKU and in normal alleles in Bulgarian families.

Haplotype	PKU alleles (n=50)	Normal alleles (n=42)
1	16	24
2	38	2
3	—	2
4	10	15
5	2	2
6	22	2
7	—	10
10	8	—
32	4	5
Others	—	38

Haplotype classification is as described.[11]

MUTATION ANALYSIS

All 29 patients (58 PKU chromosomes) were screened for five molecular defects reported to be common or relatively common in other European populations. The data are shown in table 2.

The C to T transition in codon 408, resulting in a Trp for Arg substitution, was found to be the major molecular defect which occurred in 34% of all PKU alleles studied. This mutation was found in all haplotype 2 alleles and also in a single haplotype 5 chromosome.

The splicing defect in intron 12, which accounts for nearly 40% of HPA alleles in Denmark,[3] was absent in Bulgarian PKU patients. This is in agreement with the absence of haplotype 3, which has been reported to be in tight linkage with the splicing mutation.[3]

The missense mutation in exon 5, codon 158 (Arg →Gln), which constitutes about 40% of mutant haplotype 4 alleles in western Europeans,[13 14] was detected in a single chromosome in the present study. Haplotype assignment was not fully possible in this family, but informative RFLPs (*Bgl*II, *Pvu*IIa, and *Pvu*IIb) were compatible with haplotype 4, and the polymorphic *Alu*I site in exon 7 which is typical of haplotype 4[18] was also present.

Another missense mutation, the G to A transition in codon 261 (Arg→Gln), was carried by two mutant chromosomes, both haplotype 1. Thus the mutation in codon 261 is similar in frequency to other European populations.[14] In vitro expression studies have shown

Table 2 Mutations found in Bulgarian PKU patients.

Haplotype	Cod158	Cod261	Cod281	Cod408	Unknown	Total
1		2	1		5	8
2				19		19
4	1				5	6
5				1		1
6					11	11
10					4	4
32					2	2
Not assignable					7	7

that this defect results in no detectable loss of activity.[14] In the present study both patients with $Arg^{261} \rightarrow Gln^{261}$ substitution were compound heterozygotes, for the common defect in codon 408 in one case and for an unknown defect linked to haplotype 6 in the other. Although phenylalanine tolerance has not been established yet, both patients had high neonatal phenylalanine levels, a protein loading curve with sustained high phenylalanine levels, and residual PAH activity below 1%.

The amino acid substitution in codon 281 (Pro→Leu) was detected in a single haplotype 1 chromosome. This defect has been reported to account for over 25% of mutant haplotype 1 alleles in the German population.[15]

Discussion

Both RFLP haplotypes and mutations in Bulgarian PKU patients differ in distribution from other Caucasian populations.

About 90% of the PKU alleles in northern European populations are confined to haplotypes 1 to 4,[1 5-7] whereas in Bulgarian PKU patients these haplotypes account for 64% of mutant alleles. The difference is mainly related to the total absence of haplotype 3, which is very common in Denmark[1] and gradually declines in frequency in the south and east of Europe.

A significant proportion of PKU alleles in this study belong to haplotype 6. This polymorphic haplotype is almost absent in northern Europeans, but has been reported to occur frequently in Turkish PKU patients.[19] Haplotype 6 alleles accounted for about 30% of chromosomes with an unknown mutation in this study. This haplotype is in linkage disequilibrium with the disease and may therefore be associated with a single molecular defect.

As in other Caucasian populations,[1 5-7] haplotypes 1 and 4 were found to be relatively common in Bulgarian PKU patients. Screening for three mutations, which have been previously detected in Caucasian chromosomes of these haplotypes, failed to show the molecular defect responsible in nearly 70% of these alleles. The lack of linkage disequilibrium between these haplotypes and PKU is a consistent finding in all European populations. This fact and the existence of interpopulation differences shown in this study suggest that haplotypes 1 and 4 may be very heterogeneous, not only in terms of clinical phenotype, but also in terms of molecular defects leading to classical PKU.

The present findings are further evidence of the heterogeneous molecular basis of phenylketonuria and suggest that various mechanisms might have played a role in its spread. Unlike the common mutations in codon 408 and in the 5′ splicing site of intron 12, which probably spread through founder effect, mutations linked to haplotypes 1 and 4 can be expected to be heterogeneous and to vary between populations.

This study also indicates that the use of molecular genetics as an aid to early clinical diagnosis is not feasible in Bulgarian PKU families at present. The use of five pairs of ASOs has shown both mutations in five out of 29 patients, four homozygous for the defect in codon 408 and one compound heterozygote (cod261/cod408). If haplotype 6 is indeed associated with a single mutation, as suggested by the presence of linkage disequilibrium, the proportion of informative cases will increase when this mutation becomes known; two patients in the present study are haplotype 6 homozygotes and three are 2/6 compounds. In the meantime, haplotype 6 in the homozygous state or in combination with haplotype 2 can be tentatively regarded as indicative of classical PKU, especially in patients of Turkish origin.

Although PKU is a treatable condition, our experience has shown that the majority of families are interested in prenatal diagnosis in future pregnancies. Taking into account the limited number of cases where direct mutation detection is applicable (17% of families are fully informative and 45% are partially informative), RFLP analysis has to be regarded as the main diagnostic tool. Most PKU carriers are RFLP heterozygotes, which results in almost 90% of families being fully informative for fetal RFLP analysis.

This study was supported by the Deutsche Forschungsgemeinschaft, the Bundesministerium für Forschung und Technologie, and by the Bulgarian Neurosciences and Behaviour Research Programme. LK was a fellow of the Alexander von Humboldt Foundation. The cDNA probe hpPAH247 was kindly provided by Dr S L C Woo.

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Published in final edited form as:
Mol Genet Metab. 2012 September ; 107(1-2): 3–9. doi:10.1016/j.ymgme.2012.07.005.

Nutritional Treatment for Inborn Errors of Metabolism: Indications, Regulations, and Availability of Medical Foods and Dietary Supplements Using Phenylketonuria as an Example

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Abstract

Medical foods and dietary supplements are used to treat rare inborn errors of metabolism (IEM) identified through state-based universal newborn screening. These products are regulated under Food and Drug Administration (FDA) food and dietary supplement statutes. The lack of harmony in terminology used to refer to medical foods and dietary supplements and the misuse of words that imply that FDA regulates these products as drugs have led to confusion. These products are expensive and, although they are used for medical treatment of IEM, third-party payer coverage of these products is inconsistent across the United States. Clinicians and families report termination of coverage in late adolescence, failure to cover treatment during pregnancy, coverage for select conditions only, or no coverage. We describe the indications for specific nutritional treatment products for IEM and their regulation, availability, and categorization. We conclude with a discussion of the problems that have contributed to the paradox of identifying individuals with IEM through newborn screening but not guaranteeing that they receive optimal treatment. Throughout the paper, we use the nutritional treatment of phenylketonuria as an example of IEM treatment.

Keywords

inborn errors of metabolism; inherited metabolic disorders; phenylketonuria; PKU; medical food; treatment

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1. Introduction[1]

Inborn errors of metabolism (IEM) include inherited biochemical disorders in which a specific enzyme defect interfers with the normal metabolism of protein, fat, or carbohydrate. As a result of diminished or absent enzyme activity in these disorders, certain compounds accumulate in the body to toxic levels and the levels of others that the body normally makes may become deficient. If they are not treated, these metabolic disturbances can lead to a host of medical and developmental consequences ranging from intellectual disability to severe cognitive impairment and even death. Through early identification and initiation of treatment, many of the adverse outcomes of IEM can be mitigated or prevented. For many IEM, treatment strategies rely on the provision of specialized medical foods and dietary supplements [1].

State-based universal newborn screening, one of the most successful preventive public health programs in the United States [2], identifies infants affected by IEM. See Table 1 for the Recommended Uniform Screening Panel that the Secretary of Health and Human Services (HHS) recommends for newborn screening. Not all of the disorders identified through newborn screening require treatment with medical foods, dietary supplements, or both. This paper focuses on IEM for which nutritional treatments serve as a primary therapy.

The Patient Protection and Affordable Care Act requires health care plans to provide coverage without cost sharing for newborn screening services, but no national policy calls for coverage of the costs of treatments. Some U.S. states pay for and provide medical foods as a part of their newborn screening program. Some other states that do not provide medical foods directly have enacted legislation that requires insurers to cover the costs of medical foods [3]. However, policies regarding coverage vary from state to state and even in states that require coverage, some exceptions and exclusions exist, such as the Employee Retirement Income Security Act exemptions to legislative mandates.

In this paper, we describe the indications for specific nutritional treatment products for IEM and discuss the regulation, availability, and categorization of these products. Throughout the paper, we use the nutritional treatment of phenylketonuria (PKU) as an example of IEM treatment.

2. Phenylketonuria

2.1 Characteristics and Incidence

PKU is one of a class of hyperphenylalaninemia and is the most common IEM requiring nutritional treatment. It was the first disorder to be included in state-based newborn screening programs. PKU is an autosomal recessive disorder caused by insufficient or absent phenylalanine hydroxylase, the enzyme that converts the amino acid phenylalanine (Phe) to tyrosine (Tyr). Phe builds up in the blood and brain and Tyr becomes deficient. These metabolic abnormalities lead to toxic levels of brain Phe; inadequate neurotransmitter synthesis; intellectual disability; and abnormal motor, neurocognitive, and behavioral outcomes.

The incidence of PKU in the United States is between 1 in 13,500 and 1 in 19,000 [4, 5]. Currently, an estimated 300 of the 4.2 million babies born annually in the United States are

[1]IEM: inborn error of metabolism; HHS: Health and Human Services; PKU: phenylketonuria; Phe: phenylalanine; Tyr: tyrosine; DRI: Dietary Reference Intake; FDA: Food and Drug Administration; CMS: Centers for Medicare and Medicaid Services; HCPCS: Healthcare Common Procedure Coding System

diagnosed with PKU. Over 20 years, the total number of individuals living with PKU in the United States would be about 6,000.

2.2 Nutritional Treatment

Nutritional treatment for PKU was first used successfully in 1951, prior to the implementation of state public-health newborn screening programs (http://www.youtube.com/watch?v=OqZ7QHO5_hs). Since that time, nutritional treatment for PKU has been refined and is the mainstay of treatment for PKU [6]. When initiated within the first weeks of life and maintained throughout life, an appropriately designed nutritional treatment regimen can enable individuals with PKU to achieve and maintain normal intellectual development.

Phe is an essential amino acid, meaning that it cannot be made in the human body and must be obtained from food sources. Phe's essential nature has allowed for the development of nutritional treatment for PKU that remains the standard of practice today. Dietary Phe from intact protein sources can be restricted to the amount that allows for normal growth and development while preventing excessive build-up of Phe in the blood. A dietitian with special training develops an individualized diet plan for each person with PKU. The plan is adjusted over time to accommodate changes in life stage and health status. The steps to create the diet are as follows:

- Determine the amount of Phe that the individual tolerates per day based on published guidelines [1, 7] and the dietary Phe intake that maintains blood Phe levels in the desired treatment range.
- Estimate total daily protein needs, which are usually 30 percent higher than age- and sex-specific recommendations for the general population [8] in order to maintain adequate protein status for individuals with PKU [7].
- Determine daily calorie requirements based on the individual's age and sex and the amount that ensures appropriate growth or weight maintenance [8].
- Convert the amount of Phe tolerated into quantities of whole foods using Phe "exchanges" or Phe-counting systems [1, 9] (only small amounts of protein are derived from these food sources).
- Correct the large difference between the amount of intact protein tolerated per day and total daily protein needed by using medical foods that contain protein with negligible amounts of Phe or no Phe.
- Calculate the amount of medical food needed based on the product's protein content per gram, which varies by product.
- Subtract the total calories contained in the intact protein sources plus the protein-containing medical food from the total daily calorie requirement.
- Provide the remaining calories needed using foods modified to be low in protein and protein-free foods or food ingredients, such as vegetable oils and sugar.
- Divide the whole foods that contain the tolerated amount of Phe, medical foods with protein, foods modified to be low in protein, and protein-free foods into regular meals and snacks and distribute throughout the day.
- Assess the overall nutrient adequacy of the individual's actual intake. Nutrient analysis software is available that includes medical foods and foods modified to be low in protein [10]

See Table 2 for a sample daily menu for a 9-year old child with PKU. The menu includes a medical food that provides Phe-free protein; foods modified to be low in protein; and the modest allowable amount of intact protein from fruits, vegetables, and grain based products.

Although the amount of dietary Phe that individuals with PKU tolerate varies [11], clinical observation suggests that most children, adolescents, and adults with PKU tolerate between 250 and 450 mg of dietary Phe per day (personal communication, Kathleen Huntington, May 1, 2012), which is the amount of Phe in 5 to 9 grams of intact protein or 1.5 to 3 slices of bread [12]. Clearly, no individual of any age would survive if he or she consumed only this amount of protein. Medical foods and foods modified to be low in protein were developed to provide adequate nutrition for body growth and maintenance. Without these foods, the low protein and caloric intake associated with the need to restrict dietary Phe would result in malnutrition severe enough to be incompatible with life. These special foods also help people with PKU obtain sufficient calories to prevent breakdown of muscle tissue, which would release Phe into the bloodstream.

Balancing Phe tolerance with energy needs in people with PKU becomes significantly more difficult with age. An adolescent male aged 15 to 19 years requires 3,000 calories per day, yet his Phe tolerance might only be marginally higher than that of a 9-year-old child [1]. If adults with PKU do not control their dietary Phe intake through nutritional treatment, they lose neurocognitive function. Furthermore, insufficient dietary control very early in and throughout pregnancy in women with PKU results in maternal PKU syndrome, which is associated with microcephaly, intellectual disability, cardiac defects, and growth failure in offspring.

3. Nutritional Treatment Products

Nutritional products for IEM treatment include two different forms of medical foods—one containing protein without the offending amino acid(s) and the other consisting of foods that have been modified to be low in protein. For example, medical foods for PKU provide the protein required for normal growth and development with no or negligible amounts of Phe. The majority, but not all, of these products also include other nutrients (such as fat, carbohydrate, vitamins, and minerals) needed to support normal nutritional status. These medical foods provide between 85 and 90 percent of the protein needs of an individual with PKU and are therefore a critical component of PKU treatment. Foods modified to be low in protein are an alternative to foods that must be excluded from or severely limited in a PKU diet. Modified low-protein foods include breads, pasta, cereals, and baked products made with low-protein flours. People with PKU and other IEM need these products to provide energy and satiety.

For many IEM, single amino acids and amino acid mixtures, vitamins, and other compounds are used to replace conditionally essential nutrients or enhance enzyme activity. For example, arginine must be supplemented in the diets of individuals with certain urea cycle disorders because their bodies produce insufficient amounts.

3.1 Product Terms

The products used to treat IEM are referred to in the literature and by clinicians, patients and families, and manufacturers using a variety of terms. The inconsistent use of terms has led to confusion and misunderstanding regarding the clinical purposes of these products and this misunderstanding, in turn, affects access to these treatments.

The products used to treat IEM can be broadly categorized by purpose as follows: 1) those that provide the bulk of nutritional intake for individuals with an IEM, specialized for a

specific disorder, and include protein and a range of other nutrients but not the offending amino acid(s); 2) those that are modified to be low in protein; and 3) those that are single amino acids, amino acid mixtures, vitamins, or other compounds used to replace conditionally essential nutrients or to enhance enzyme activity. A more detailed description of these products, their intended use, and companies that manufacture and/or distribute them follows in Sections 3.1.1 and 3.1.2 and Table 3 below.

3.1.1 Medical Foods

1. Products that provide protein and varying amounts of carbohydrate, fat, vitamins, and minerals. Additional terms that may be used to describe these products include medical formulas, medical protein options, medical protein, protein substitutes, and deficient protein. These products are generally not available at retail outlets. See Table 3 for a list of companies that manufacturer and/or distribute medical foods with protein for infants, children, adolescents, and adults in the United States.
    a. For infants:
        i. Powdered formulas contain all the nutrients required for growth and development, *except* the offending nutrient(s). For example, products for PKU exclude Phe.
        ii. Calculated amounts of breast milk or standard infant formula must be added to provide the amount of Phe required for growth and development.
    b. For children over age 1 year, adolescents, and adults:
        i. Some products have a full complement of nutrients *except* the offending nutrient(s). For example, products for PKU exclude Phe or have negligible amounts. These products are available in the following formats:
            1. Powdered form that must be reconstituted with water or juice.
            2. Ready to consume (liquid products may be concentrated low volume).
            3. Bars.
        ii. "Modular" products have separate components, such as packets of amino acid mixtures, tablets, bars, and sports drinks without the offending amino acids(s) and limited or no vitamins and minerals; vitamin and mineral preparations; and liquid and powdered medium-chain triglycerides.
        iii. Sources of intact protein to provide the required amount of Phe needed for growth and development must be added to the diet using calculated amounts of fruits, some vegetables and grains, and foods modified to be low in protein.
2. Foods modified to be low in protein.
    a. These foods are designed for infants (as age appropriate), children, adolescents, and adults with IEM, such as PKU, maple syrup urine disease, organic acidurias, and urea cycle disorders.

b. These products are manufactured to be low in protein as an acceptable alternative to a standard food that must be excluded from the patient's diet or that the patient could otherwise consume only in minimal amounts.

c. Examples include flour; cereals; baked goods, such as bread, cookies, crackers, and pizza dough; "peanut butter" spread; meat and cheese substitutes; pasta; and rice.

d. See Table 3 for a list of companies that manufacture and/or distribute foods modified to be low in protein in the United States.

3.1.2 Single Amino Acids and Amino Acid Mixtures, Vitamins, and Other Compounds Used to Replace Conditionally Essential Nutrients or Enhance Enzyme Activity

1. For PKU, Tyr is conditionally essential and must be supplemented through a medical food or a single amino acid. Patients with other IEM need similar supplementation of amino acids that become conditionally essential when they are not produced by the abnormal enzyme system (e.g., arginine or citrulline in urea cycle disorders).
2. For other IEM (e.g., glutaric aciduria, maple syrup urine disease, and homocystinuria), vitamins (e.g., riboflavin, thiamin, biotin, cobalamin, pyridoxine, and folic acid) that serve as cofactors in enzyme systems must be provided in doses exceeding the Dietary Reference Intake (DRI). Which vitamins patients need in high doses depends on the disease and whether the patient has residual enzyme activity. The use of these products requires medical management and monitoring.
3. Some IEM require supplementation with carnitine (e.g., for organic acidurias) or betaine (e.g., for homocystinuria).

3.2 Product Regulation

3.2.1 Medical Foods for Infants—In the United States, the Food and Drug Administration (FDA) regulates infant formulas developed for IEM and categorizes these formulas as "exempt." These formulas must meet the same regulatory requirements as standard infant formulas, except that FDA does not require them to include the offending nutrient(s); for example, products designed for PKU do not include Phe [13].

The term "exempt" may be misleading because it implies that these formulas are exempt from all regulations, which is not the case. Manufacturers must provide a detailed description of the medical condition that the formulas are designed to treat, the rationale for the deviation from a standard infant formula, and a specific disease claim for the product's use (e.g., for use in PKU) [13]. New exempt infant formulas require a 90-day premarket notification to FDA by the manufacturer. The exempt infant formulas used to manage IEM are generally represented and labeled solely to provide dietary management for a disease or condition that is clinically serious or life-threatening and patients must use these formulas for prolonged periods [14]. Although infant formulas for IEM are also considered to be medical foods (discussed in Section 3.2.2 below), they are regulated as infant formulas.

3.2.2 Medical Foods for Children and Adults—Medical foods for children over age 1 year and for adults are designed to treat a specific condition, so they are exempt from the nutrition labeling, health claims, and nutrient content claims requirements of the Nutrition Labeling and Education Act of 1990 [15]. They must, however, meet the requirements of good manufacturing practices.

Products manufactured for the nutritional treatment of IEM are considered medical foods as defined by the Orphan Drug Amendments of 1988 [16]:

> … a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

Further information on the definition of a medical food is available in FDA's *Compliance Program Guidance Manual,* which includes the following expanded definition [17]:

> Generally, to be considered a medical food, a product must, at a minimum, meet the following criteria:
>
> **a.** The product is a food for oral or tube feeding;
>
> **b.** The product is labeled for the dietary management of a medical disorder, disease, or condition; and
>
> **c.** The product is labeled to be used under medical supervision, and is primarily obtained through hospitals, clinics, and other medical and long term care facilities.
>
> *Medical foods are distinguished from the broader category of foods for special dietary use and from foods that make health claims by the requirement that medical foods are to be used under medical supervision.* ***The term "medical foods" does not pertain to all foods fed to sick patients. Medical foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in its natural state) for the patient who is seriously ill or who requires the product as a major treatment modality****. Typical medical foods are enteral nutrition products, i.e., products provided through the gastrointestinal tract, taken by mouth, or provided through a tube or catheter that delivers nutrients beyond the oral cavity or directly to the stomach.* [Boldface added for emphasis by the authors.]

Foods modified to be low in protein are manufactured specifically for protein-restricted diets that require medical supervision, such as the diets that people with PKU must follow. These foods are generally labeled as such.

Medical foods (with the exception of infant formulas, as discussed in Section 3.2.1 above), including foods modified to be low in protein, do not require premarket review and are not registered with FDA [18]. However, like all food manufacturers, manufacturers that make medical foods must be registered with and are inspected by FDA [19].

3.2.3 Dietary Supplements—Single amino acids and amino acid mixtures, vitamins, and other compounds are often used to replace conditionally essential nutrients or enhance enzyme activity in patients with IEM. FDA classifies single amino acids, amino acid mixtures, vitamins, and several other compounds used to treat IEM as dietary supplements. These products must meet the requirements of the Dietary Supplement Health and Education Act [20]. Generally, manufacturers do not need to register these products with FDA or obtain FDA approval before producing or selling them. However, manufacturers are responsible for ensuring that the dietary supplements they manufacture are safe before marketing these products. FDA may take action against any unsafe dietary supplement product after that product reaches the market.

L-carnitine, a product used in specific IEM to replace this conditionally essential nutrient and/ or assist in the excretion of toxic metabolites, can be obtained as both a prescription drug (Carnitor® by Sigma Tau) and a dietary supplement.

With the exception of Carnitor®, FDA does not regulate dietary supplements used to replace conditionally essential nutrients or enhance enzyme activity in patients with IEM as drugs. These products are, however, often given to patients in doses that far exceed DRI levels and their use in IEM closely approximates the action of drugs. The term "pharmacological dose" is often used to describe the large doses of dietary supplements used in IEM. However, strictly speaking, the term "pharmacologic" is misapplied to these products because they are not defined or regulated as drugs in the United States.

3.3 Availability and Distribution

In general, and, with the exception of federal health insurance programs, such as TRICARE® (the health care program for uniformed service members, retirees, and their families), what is covered by insurers is determined by state regulations and policies. No national or uniform policy addresses coverage for medical foods for individuals with IEM. Individuals with IEM, including PKU, obtain medical foods through a number of mechanisms, including distribution programs associated with metabolic clinic and state newborn screening programs, pharmacies, home health care companies that provide durable medical equipment supplies, and manufacturer ordering programs. The source used to obtain medical food products depends on where the patient lives and whether third-party payers cover the products' costs.

Dispensing entities and manufacturers typically require authorization from a medical professional before dispensing a medical food to a patient to prevent inappropriate use of these products. The authorization for the product from a medical professional specifies the amount of medical food that the patient needs based on his or her age and nutritional requirements. This authorization is often written as a "prescription." However, these products are not regulated as drugs and the use of the term "prescription" has been a source of confusion with respect to reimbursement. Clinicians recommend foods modified to be low in protein but patients typically purchase these products through mail order without needing to obtain medical authorization first.

3.4 Public and Private Insurance Coverage of Medical Foods

As per FDA regulation, medical foods are formulated to be consumed or administered enterally and are consumed orally or through a tube. Most individuals with IEM consume their medical food treatments by mouth. However, the Centers for Medicare and Medicaid Services (CMS) Healthcare Common Procedure Coding System (HCPCS) coding for provision of enteral formulas designates administration by feeding tube. In addition, the amount of medical food needed by many individuals with IEM is typically calculated based on grams of protein, yet CMS coding is based on calories. These discrepancies further exacerbate the reimbursement problem. See https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads//ncd103c1_Part3.pdf for coverage regulations. Of note is that CMS does not include the term "medical food" in its HCPCS coding language.

Some states provide coverage of medical foods for people with IEM through their state public health newborn screening programs. Thirty-eight states have enacted legislation that requires insurers to provide coverage for medical foods for at least PKU; over a third of these states require coverage for all IEM [21]. States generally do not provide coverage

beyond the age of 18 [5]. Three-quarters of states that have passed mandates require coverage for foods modified to be low in protein [21].

Insurance coverage is subject to the limitations of each policy, including co-payments, cost-sharing requirements, and deductibles. In addition, federal programs such as TRICARE® and policies that are certified by the Employee Retirement Income Security Act (or are self-insured) do not need to comply with state mandates. Medicaid covers the costs of medical foods in all but one state. Foods modified to be low in protein are less widely covered by third-party payers.

3.5 Estimated Costs for Medical Foods

The estimated annual wholesale costs of medical foods supplying protein (excluding additional costs for foods that are modified to be low in protein, amino acids, vitamins, and other compounds) for amino acid disorders identified by state-based, universal newborn screening are shown in Table 4. For PKU, the average wholesale cost to supply DRI levels of protein [21] during the first year of life is estimated to be $1,248. As protein requirements increase into adulthood, the wholesale cost of medical foods supplying protein increases to an estimated $8,522 for late adolescent and adult males and during pregnancy.

Patients and insurance companies typically pay more than the wholesale cost for medical foods. Third-party durable medical equipment vendors and pharmacies increase the billed costs to insurance companies by as much as 200 to 300 percent of the wholesale cost. In some cases, families pay more than the wholesale price (through coinsurance) for products that insurance companies obtain through third-party vendors.

Foods modified to be low in protein cost two to eight times as much as their regular counterparts. These foods are rarely available in retail stores, and their shipping and handling costs can be as high as $50.00. See Table 5 for examples of the costs of regular food options compared to the costs of similar foods modified to be low in protein.

4. Discussion

Virtually every newborn in the country is screened early to identify IEM and other disorders through universal state-based newborn screening programs. These programs began over half a century ago and have expanded over the years to identify more than 30 disorders. Most IEM that require medical foods are detected through these efforts. Nutrition treatment is the standard of medical care for many disorders identified through newborn screening, yet affected individuals do not necessarily have access to appropriate treatment. Systemic problems that have contributed to this paradox include the lack of robust, evidence-based research documenting the effectiveness of treatments and inconsistent access to these treatments.

Individual IEM are rare and each has a unique etiology, pathophysiology, and response to therapeutic interventions. IEM are generally identified in infancy and have a very narrow window of treatment opportunity. Randomizing patients with IEM into treatment or control arms in clinical trials is generally not possible because assigning infants or children with IEM to a placebo group would be unethical. Although efforts are underway to evaluate the evidence and design nutritional guidelines for IEM treatment, little information in this area of patient management has come from rigorous, controlled research studies. In this era of health care reform, a greater investment in evidence-based research for the treatments used in IEM has become critical.

Nutritional treatments are regulated under FDA food and dietary supplement regulations, not regulations that govern "drugs." Unlike regulated drugs, these treatments do not require a "prescription." They are viewed as "food" and "supplements," which exacerbates the difficulty of obtaining third-party payer reimbursement for these products. In addition, the use of inconsistent terminology when referring to medical foods and dietary supplements and the misuse of words that imply that these products are regulated as drugs lead to confusion. The appropriate and effective use of medical foods and select dietary supplements for IEM is constrained by discrepancies in terminology and misunderstanding regarding the regulation of these products.

Although 38 states require coverage of medical foods by third-party payers, many inconsistencies and loopholes remain in medical food coverage. Currently, a patchwork of coverage exists, ranging from selective coverage of medical foods for specific disorders, termination of benefits in late adolescence, failure to cover treatment during pregnancy, and restrictions on the types of medical foods covered, to caps on the dollar amount covered.

In April 2009, the HHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children recommended insurance coverage for IEM, tying their recommendation for coverage to the Secretary's recommended uniform screening panel (which is covered by the Patient Protection and Affordable Care Act) [22]. The committee characterized individuals identified through newborn screening who require specific treatments to be at high risk and recommended that HHS regulations ensure that these individuals have access to comprehensive treatment coverage.

Access to treatment for IEM is an essential component of the of the public health newborn screening system, the goal of which is to prevent adverse outcomes in individuals who are affected by these disorders. Improving patient access to nutritional treatments for IEM should start by harmonizing definitions and interpretations of statutes used to describe and regulate nutritional treatments for IEM. Educating state policymakers about nutritional treatments for IEM could lead to improved health insurance coverage of IEM treatments.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the NIH or the US Department of Health and Human Services.

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Highlights

- We define medical foods and dietary supplements and their regulation.
- Nutrition treatment is standard of medical care for inborn errors of metabolism.
- Medical foods and dietary supplements are not regulated as drugs.
- Insurance coverage for nutrition treatment varies based on state insurance mandates.
- We suggest ways to improve patient access to nutrition treatments.

Table 1

Core conditions screened in the newborn period categorized by screening methodology and family of disorder.

Tandem Mass Spectrometry				
Acylcarnitines				
Organic Acidurias	**Fatty Acid Oxidation**	**Amino Acids**	**Hematology**	**Others**
Isovaleric acidemia	**Medium-chain acyl- CoA dehydrogenase deficiency**	**Phenylketonuria**	Sickle cell anemia	Congenital hypothyroid
Glutaric acidemia type I	**Very long-chain acyl- CoA dehydrogenase deficiency**	**Maple syrup (urine) disease**	Hb S/β thalassemia	**Biotinidase**
3-Hydroxy 3 –methyl glutaric aciduria	**Long-chain L-3- hydroxyacyl-CoA dehydrogenase**	**Homocystinuria**	Hb S/C disease	Congenital adrenal hyperplasia
Multiple carboxylase deficiency	**Trifunctional protein deficiency**	**Citrullinemia**		Classical galactosemia
Methylmalonic acidemia	**Carnitine uptake defect**	**Argininosuccinic aciduria**		Hearing loss
3-Methylcrotonyl-CoA carboxylase deficiency		**Tyrosinemia type I**		Cystic fibrosis
Propionic acidemia				Severe combined immunodeficiency
β-Ketothiolase				

Diseases in bold are treated with medical foods and/or single amino acids and amino acid mixtures, vitamins, and other compounds. Terminology consistent with [23].

Table 2

Sample daily menu for a 9-year-old child with PKU.

Meal	Food Item	Protein g	Phe mg	Calories
Breakfast	1 low-protein bagel (53 g)	0.4	21	110
	2 tablespoons low-protein peanut butter spread (36 g)	0.1	8	230
	8 fluid ounces medical food with Phe-free protein	14	0	190
Lunch	5 raw, baby, medium-size carrots (50 g)	0.3	15	20
	Low-protein chicken soup broth with low-protein pasta	0.3	4	61
	5 low-protein saltine crackers (31 g)	1.5	3	138
	1 medium-size apple (138 g)	0.3	15	81
	8 fluid ounces medical food containing Phe-free protein	14	0	190
Snack	1 fresh pear (166 g)	0.3	17	98
	12 Pepperidge Farm Goldfish (6 g)	1.0	45	27
Dinner	1 low-protein veggie burger (71 g)	1.3	50	80
	1 low-protein bun (80 g)	0.3	6	130
	3 tablespoons catsup (45 g)	0.3	15	48
	8 fluid ounces medical food with Phe-free protein	14	0	190
	9 French fries (60 g)	1.0	45	132
	3 tablespoons corn, cooked, cut kernels (30 g)	1.0	45	24
	1 low-protein chocolate chip cookie (28 g)	0.2	3	120
	Totals	**50**	**292**	**1,870**

Phe = phenylalanine

This sample meal plan provides about 300 mg dietary Phe, 50 g total protein, and 1,900 calories. The intact protein sources (regular foods) supply 4.2 g protein as well as two-thirds of the dietary Phe and 23 percent of the calories in the menu. The medical food containing Phe-free protein provides 42 g protein and 570 calories. The foods modified to be low in protein provide another 4 g protein and the remaining dietary Phe. The medical foods contribute 92 percent of the protein and 77 percent of the calories that this child needs.

Table 3

Medical food manufacturers and distributors.

Company	Website	Medical Foods with Protein		Medical Foods Modified to be Low in Protein
		For Infants	For Children, Adolescents, and Adults	
Abbott Nutrition 3300 Stelzer Road Columbus, OH 43219	http://abbottnutrition.com/Infant-And-New-Mother/Infant-Metabolic-Disorder-Products.aspx	x	x	
Applied Nutrition 10 Saddle Road Cedar Knolls, NJ 07927	http://www.medicalfood.com/		x	x
Cambrooke Foods, Inc. 4 Copeland Drive Ayer, MA 01432	http://www.cambrookefoods.com/		x	x
Dietary Specialties 8 South Commons Road Waterbury, CT 06704	www.dietspec.com			x
Ener-G Foods, Inc. 5960 First Ave S. Seattle, WA 98108	www.ener-g.com			x
Mead Johnson Nutrition 2400 West Lloyd Expressway Evansville, IN 47721	http://www.meadjohnson.com/Brands/Pages/Products-by-Need.aspx	x	x	
Nutricia, North America PO Box 117 Gaithersburg, MD 20884	http://www.nutricia-na.com/pages/metabolics_glance.htm	x	x	x
PKU Perspectives 472 South 640 West Pleasant Grove, UT 84062	www.pkuperspectives.com		x	x
Solace Nutrition	www.solacenutrition.com		x	

Company	Website	Medical Foods with Protein		Medical Foods Modified to be Low in Protein
		For Infants	For Children, Adolescents, and Adults	
10 Alice Court Pawcatuck, CT 06379				
Taste Connection 612 Meyer Lane #13 Rehondo Beach, CA 90278	www.tasteconnections.com			x
Vitaflo 211 North Union Street Alexandria, VA 22314	http://www.vitaflousa.com/products/		x	x

Table 4

Average annual wholesale costs for medical foods with protein in 2010 for select newborn screened disorders supplying Dietary Reference Intake age-based protein requirements [8].

Estimated Average Costs ($) for Age-Based Protein Requirements per Year for Select Disorders Screened in the Newborn Period[a]										
Age in years	**DRI protein requirements in grams (g)**	**PKU**	**PA**	**MMA**	**HCY**	**MSD**	**GA 1**	**Tyr-1**	**IVA**	**Average**
Less than 1	10	1,248	1,900	1,900	1,747	1,766	1,970	1,963	2,074	1,817
1–3	13	1,806	2,745	2,745	2,524	2,551	2,845	2,836	2,991	2,520
4–8	19	2,643	3,494	3,494	3,689	3,728	3,054	3,730	3,817	3,456
9–13	34	4,829	6,252	6,252	5,816	6,185	6,488	7,111	7,060	6,249
Males 14–18	52	7,386	9,537	9,537	8,895	9,459	9,922	10,876	10,798	9,551
Females 14 to older than 70	46	6,534	8,436	8,436	8,513	8,368	8,777	9,621	9,552	8,530
Males 19 to older than 70 and pregnant females	60	8,522	11,004	11,004	10,264	10,915	11,449	12,549	12,459	11,021

DRI = Dietary Reference Intake; PKU = phenylketonuria; PA = propionic academia; MMA = methylmalonic academia; HCY = homocystinuria; MSD = maple syrup disease; GA1 = glutaric aciduria, type 1; Tyr-1 = tyrosinemia, type 1; IVA = isovaleric academia

[a]The average cost for the medical foods with protein is based on the individual wholesale cost of a selection of products manufactured to treat each disorder. The cost associated with the amount of product providing a specific amount of protein was determined for each product and then averaged across all products.

Table 5

Costs of selected foods modified to be low in protein and their regular counterparts.

Regular Food Option[a]	Cost per 100 g Product in Dollars[b]	Low-Protein Version	Cost per 100 g Product in Dollars[b,c]
Spaghetti	0.37	Aproten low protein pasta	2.20
Flour	0.17	Wel-Plan baking mix	1.29
Bisquick®	0.31	Taste Connections low protein baking mix	0.58
Crackers	0.64	Loprofin crackers	1.94
Tortillas	0.40	Low-pro tortillas	2.04
Peanut butter	0.70	Low-pro peanut spread	1.94

[a] Contains 10 to 40 times more protein than low-protein versions.

[b] Shipping charges range from none (with purchases over $30) to $50.00, depending on the company.

[c] Low-protein versions cost 2 to 8 times more than regular food options.