PIANO DI LAVORO

Gruppo di Studio “Dietoterapie in epilessia”

Progetto : Studio osservazionale

Centro coordinatore

Ricercatore Principale	Prof. Pierangelo Veggiotti
Centro Coordinatore:	Struttura Complessa di Neuropsichiatria Infantile “Istituto Neurologico Nazionale C. Mondino” - Pavia
Telefono	0382/380344 -289
Fax	0382/380286
E-mail	pveggiot@unipv.it
Durata	24 – 36 mesi

INDICE

Introduzione

A partire dal lavoro già effettuato che ha permesso di elaborare un consenso italiano sull'utilizzo della dieta chetogenica alla cui stesura ha partecipato un gruppo di lavoro con competenze varie (Pierangelo Veggiotti, Alberto Burlina, Giangennaro Coppola, Raffaella Cusmai, Renzo Guerrini, Anna Tagliabue, Bernardo Dalla Bernardina) si propone di utilizzare tale consensus (vedi allegato) come base di partenza per raccogliere dati omogenei relativi all'utilizzo della dieta chetogenica.

Obiettivi

Obiettivo principale è quello di uniformare i criteri e le modalità di utilizzo della dieta, secondo il consensus italiano, nelle strutture specialistiche, a competenza elevata e con specifica esperienza epilettologica, da trasferire alle strutture neuropsichiatriche, neuropediatriche e pediatriche del territorio nazionale.

Obiettivo secondario sarà la raccolta centralizzata dei dati relativi l'utilizzo della dieta chetogenica che saranno maggiormente omogenei sia per le caratteristiche del campione sia per le modalità di gestione della dieta secondo il consensus italiano e la loro diffusione alla comunità scientifica .La raccolta centralizzata dei dati permetterà di avere dati relativi ad un campione più ampio e maggiormente confrontabile con le casistiche delle altre nazioni .

Metodologia

Disegno dello studio

Lo studio sarà suddiviso in due sottoprogetti:

- **A)** STUDIO retrospettivo
- **B)** STUDIO prospettico

Popolazione in studio

Studio A.

Verranno presi in esame in modo retrospettivo i dati relativi i pazienti che hanno utilizzato la dieta chetogenica, senza alcuna distinzione, che sono stati presi in carico dalle varie unità operative dei soci LICE negli ultimi 5-10 anni. Tali dati verranno raccolti mediante un questionario già elaborato (vedi allegato) e inseriti in un database (foglio di lavoro) centralizzato.

Studio B.

I pazienti che arriveranno alla consultazione dalla data di inizio dello studio (data di inizio da concordare con il gruppo) saranno valutati in modo prospettico. A tali pazienti sarà applicato il consensus italiano che deriva da un precedente studio di un gruppo multidisciplinare. (vedi allegato)
I dati relativi a questo gruppo di pazienti verranno raccolti mediante l'utilizzo del questionario predisposto anche per la raccolta dei dati retrospettivi.

Indicatori

Studio A

- numero di casi che hanno effettuato la dieta chetogenica
- diagnosi epilettologica
- diagnosi eziologica
- esame neurologico, ritardo mentale , reattività
- terapie farmacologiche, chirurgiche
- dati relativi la dieta chetogenica
- tipologia, frequenza e durata delle crisi
- caratteristiche minime studio elettroencefalografico (elettrofisiologico)

Studio B

Oltre agli indicatori previsti per lo Studio A, la conformità della pratica adottata rispetto al consensus italiano vs. discostamenti.

Risultati attesi

Studio A

- raccolta dei dati anamnestici e clinici
- inserimento dei dati raccolti ed elaborazione degli stessi

Studio B

- raccolta dei dati riguardanti questo gruppo di pazienti
- rilievo dei discostamenti
- confronto dei dati emersi
- confronto dei dati relativi al campione italiano con quelli della comunità scientifica internazionale

Trasferibilità dei risultati e dei prodotti

Gli obiettivi principali e secondari del progetto mettono in evidenza come la trasferibilità del prodotto risulti essere un elemento fondamentale.

Infatti l'auspicio e l'impegno del lavoro è quello di uniformare le modalità di utilizzo della dieta nei vari gruppi italiani e di raccogliere dei dati che possano quindi diventare di dominio comune alle strutture neuropsichiatriche, neuropediatriche e pediatriche del territorio nazionale.

Cronogramma

Mesi

Archiviazione della documentazione

Tutti i documenti contenenti i dati originali richiesti e trascritti sulla scheda raccolta dati rimarranno presso gli archivi dell'Istituto IRCCS "C. Mondino".

Allegati

Scheda raccolta dati

Nome centro _____
Nome operatore _____
Telefono _____
E-mail _____

Scheda di rilevazione dati
DATA DI COMPILAZIONE ___/___/____

PROGETTO RACCOLTA DATI DIETA CHETOGENICA

ID PAZIENTE |____| *(n° progressivo)*

CODICE FISCALE_____

DATA DI NASCITA ___/___/___

PROVENIENZA |__| regionale |__| extraregionale

SESSO |_M_| |_ F_|

Indicare la regione |___| *(per la codifica vedere **Allegato A**)*

DIAGNOSI EPILETTOLOGICA

DATA DELLA DIAGNOSI ____/____/_____ ***(gg/m/aaaa)***

|_A_| Epilessia focale idiopatica
|_B_| Epilessia focale sintomatica
|_C_| Epilessia generalizzata idiopatica
|_D_| Sindrome di West
|_E_| Sindrome di Dravet
|_F_| Sindrome di Lennox Gastaut
|_G_| Encefalopatia epilettogena / Sindrome catastrofica

DIAGNOSI EZIOLOGICA

DATA DELLA DIAGNOSI ____/____/_____ ***(gg/m/aaaa)***

|_A_| Idiopatica
|_B_| Criptogenetica
|_C_| Sintomatica di patologia nota
|_D_| Sintomatica di patologia non nota

Se **C definire:**
|_1_| Sindrome genetica
|_2_| Noxa pre-perinatale
|_3_| Noxa acquisita post-natale
|_4_| Malformazioni SNC
|_5_| Sindrome neurocutanea
|_6_| Difetto congenito del metabolismo

Se **4 definire:**
|_1_| Difetti generalizzati di proliferazione e differenziazione: microlissencefalia, emimegalencefalia
|_2_| Difetti focali di differenziazione e proliferazione (TSC, Displasia corticale Taylor Type)
|_3_| Difetti generalizzati della migrazione neuronale (lissencefalia, agiria, pachigiria)
|_4_| Difetti focali e multifocali della migrazione neuronale (lissencafalia parziale, eterotopia nodulare
|_5_| Difetti del'organizzazione corticale (polimicrogiria, schizencefalia)
|_6_| Displasia corticale bilaterale
|_7_| Displasia corticale focale

ESAME NEUROLOGICO

EN INIZIALE (al momento dell'introduzione della DK)
|_0_| Normale
|_1_| Patologico
|_ND_| Non eseguito

Se **1 definire:**
|_A_| Segni neurologici minori,
|_B_| Ipotonia generalizzata senza acquisizioni posturali
|_C_| Tetraparesi spastica

EN CONTROLLI SUCCESSIVI

0 = NESSUNA VARIAZIONE 1 = MODESTAMENTE MIGLIORATO 2 = NOTEVOLMENTE MIGLIORATO

Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni	Controllo a
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

RITARDO MENTALE

|_0_| Assente
|_1_| Lieve
|_2_| Medio
|_3_| Grave
|_4_| Rallentamento ideo-motorio

REATTIVITA'

0 = NELLA NORMA 2 = COMPROMESSA
1 = LIEVEMENTE RIDOTTA 3 = GRAVEMENTE COMPROMESSA

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

ETA' ALL'ESORDIO DELLE CRISI ***(in mesi)*** _____

TERAPIA

TERAPIA EFFETTUATA IN PRECEDENZA |___| *(numero farmaci utilizzati)*
Barrare quali

PB	|___|	PRM	|___|	CBZ-CR	|___|	FBM	|___|	STEROIDI	|___|
ESM	|___|	CLZ	|___|	GVG	|___|	ACTH	|___|	VPAChrono	|___|
TPM	|___|	OXC	|___|	LVT	|___|	Bromidi	|___|	STIRIPENTOLO	|___|
PHT	|___|	CBZ	|___|	VPA	|___|	Acet	|___|		
CZP	|___|	altre BZ	|___|	LTG	|___|	B6	|___|	ALTRO	|___|
GBP	|___|	TGB	|___|	ZNS	|___|	Ig	|___|	*(specificare*_____	
									_____ *)*	

TERAPIA CHIRURGICA

|_1_| Non considerata
|_2_| Pz in corso di valutazione
|_3_| Pz valutato, non idoneo
|_4_| Pz accettato per intervento
|_5_| Già effettuata
|_6_| Pz idoneo, ma rifiuta intervento
|_7_| Interventi "palliativi" (i.e. applicazione stimolatori)

TERAPIA IN CORSO (al momento dell'introduzione della DK) |__| *(numero farmaci utilizzati)*
Barrare quali

PB	|___|	TPM	|___|	CZP	|___|	PRM	|___|	OXC	|___|
ESM	|___|	PHT	|___|	GBP	|___|	CLZ	|___|	CBZ	|___|

altre BZ |___| LVT |___| FBM |___| B6 |___| STIRIPENTOLO |___|
TGB |___| VPA |___| ACTH |___| Ig |___|
CBZ-CR |___| LTG |___| Bromidi |___| STEROIDI |___| ALTRO |___|
GVG |___| ZNS |___| Acet |___| VPAChrono |___| *(specificare_____ _____)*

DK

DATA INIZIO DK ____/____/_____ ***(gg/m/aaaa)***

ETÀ' INIZIO DK ***(in mesi)*** _____

TIPO DK

|_1_| Tradizionale (4:1) |_3_| Tradizionale (3:1) |_5_| Mista
|_2_| Ketocal (4:1) |_4_| Ketocal (3:1)

TIPOLOGIA, FREQUENZA E DURATA DELLE CRISI

CRISI PRIMARIA (crisi più frequente)
TIPO

|_A_| Crisi generalizzate
|_B_| Crisi Parziali

Se **A (crisi generalizzate):**

|_1_| GTCS
|_2_| Assenze
|_3_| Spasmi
|_4_| Crisi toniche
|_5_| Crisi miocloniche
|_6_| Crisi atoniche

FREQUENZA

0 = NON CRISI
1= < 1/MESE
2 = 1-3/MESE
3 = 1-5/MESE
4 = 5-10/MESE
5 = 10-20/MESE
6 = > 20/MESE
7 = > 50/MESE
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

DURATA

0 = NON CRISI
1 = < 15 SEC
2 = < 30 SEC
3 = < 1 MIN
4 = 1-5 MIN
5 = 5-10 MIN
6 = 10-20 MIN
7 = > 20 MIN
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

CRISI SECONDARIA
TIPO

|_A_| Crisi generalizzate
|_B_| Crisi Parziali

Se **A (crisi generalizzate):**

|_1_| GTCS
|_2_| Assenze
|_3_| Spasmi
|_4_| Crisi toniche
|_5_| Crisi miocloniche
|_6_| Crisi atoniche

FREQUENZA

0 = NON CRISI
1= < 1/MESE
2 = 1-3/MESE
3 = 1-5/MESE
4 = 5-10/MESE
5 = 10-20/MESE
6 = > 20/MESE
7 = > 50/MESE
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

DURATA

0 = NON CRISI
1 = < 15 SEC
2 = < 30 SEC
3 = < 1 MIN
4 = 1-5 MIN
5 = 5-10 MIN
6 = 10-20 MIN
7 = > 20 MIN
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

CRISI TERZIARIA

TIPO

|_A_| Crisi generalizzate
|_B_| Crisi Parziali

Se **A (crisi generalizzate):**

|_1_| GTCS
|_2_| Assenze
|_3_| Spasmi
|_4_| Crisi toniche
|_5_| Crisi miocloniche
|_6_| Crisi atoniche

FREQUENZA

0 = NON CRISI
1= < 1/MESE
2 = 1-3/MESE
3 = 1-5/MESE
4 = 5-10/MESE
5 = 10-20/MESE
6 = > 20/MESE
7 = > 50/MESE
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

DURATA

0 = NON CRISI
1 = < 15 SEC
2 = < 30 SEC
3 = < 1 MIN
4 = 1-5 MIN
5 = 5-10 MIN
6 = 10-20 MIN
7 = > 20 MIN
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

EEG

Se necessario, segnare più di una voce per casella.

0 = NELLA NORMA
1 = NORMALE AF, POCHE ANOMALIE
2 = NORMALE AF, ANOMALIE FREQUENTI
3 = AF LENTA, POCHE ANOMALIE
4 = AF LENTA, ANOMALIE FREQUENTI
5 = AF LENTA, ANOMALIE SUBCONTINUE
6 = COME PRECEDENTE
7 = REGISTRAZIONE CRISI
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

EFFETTI COLLATERALI

Se necessario, segnare più di una voce per casella.

0 = NESSUNO
1= LETARGIA (ipoglicemia)
2 = SINTOMI GI
3 = ALTERAZIONI METABOLICHE
4 = PERDITA PESO
5 = LINGUA NIGRA
6 = CALCOLI RENALI
7 = ALTRO *(specificare_____)*
ND = dato non disponibile

Inizio DK (tempo 0)	Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

RISPOSTA ALLA TERAPIA

1 = Scomparsa totale crisi
2 = Riduzione crisi > 50%

3 = Riduzione crisi < 50%
4 = Nessuna modificazione della frequenza critica

5 = Non valutabile
6 = Non applicabile

Controllo a 1 mese	Controllo a 3 mesi	Controllo a 6 mesi	Controllo a 9 mesi	Controllo a 12 mesi	Controllo a 15 mesi	Controllo a 2 anni	Controllo a 3 anni	Controllo a 5 anni	Controllo a
Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a	Controllo a

DIETA ATTUALMENTE IN CORSO |_sì_| |_no_|

Se **no indicare:**

DATA SOSPENSIONE DK ____/____/_____ ***(gg/m/aaaa)***

CAUSA SOSPENSIONE

|_A_| Inefficacia
|_B_| Non compliance
|_C_| Effetti collaterali GI
|_D_| Effetti collaterali metabolici
|_E_| Altro *(specificare*_____*)*

ALLEGATO A – CODIFICA REGIONI

CODIFICA REGIONI

VALLE D'AOSTA	= 1
PIEMONTE	= 2
LOMBARDIA	= 3
LIGURIA	= 4
VENETO	= 5
TRENTINO	= 6
FRIULI V.G.	= 7
EMILIA ROMAGNA	= 8
TOSCANA	= 9
MARCHE	= 10
UMBRIA	= 11
LAZIO	= 12
ABRUZZO	= 13
MOLISE	= 14
CAMPANIA	= 15
PUGLIA	= 16
BASILICATA	= 17
CALABRIA	= 18
SICILIA	= 19
SARDEGNA	= 20
ESTERO	= 21

Consensus italiano

Epilepsia, 52(Suppl. 2):83–89, 2011
doi: 10.1111/j.1528-1167.2011.03010.x

DRAVET SYNDROME

The ketogenic diet for Dravet syndrome and other epileptic encephalopathies: An Italian consensus

*Pierangelo Veggiotti, †Alberto Burlina, ‡Giangennaro Coppola, §Raffaella Cusmai, *Valentina De Giorgis, ¶Renzo Guerrini, **Anna Tagliabue, and ††Bernardo Dalla Bernardina

*Department of Child Neurology and Psychiatry, Fondazione IRCCS Istituto Neurologico C. Mondino, Pavia, Italy; †Division of Inborn Metabolic Diseases, Department of Pediatrics, University Hospital Padova, Padova, Italy; ‡Department of Child Neuropsychiatry, University of Naples, Naples, Italy; §Division of Neurology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; ¶Pediatric Neurology Unit and Laboratories, Children's Hospital A. Meyer, University of Florence, Florence, Italy; **Nutrition and Eating Disorder Research Center, University of Pavia, Pavia, Italy; and ††Unit of Child Neuropsychiatry, University of Verona, Verona, Italy

Summary

Ketogenic diet is a nonpharmacologic treatment for childhood epilepsy not amenable to drugs. At the present time, two works based on national research, one in Germany and one in the United States provide international guidelines to ensure a correct management of the ketogenic diet. Our Italian collaborative study group was set up in order to formulate a consensus statement regarding the clinical management of the ketogenic diet, patient selection, pre–ketogenic diet, counseling, setting and enforcement of dietary induction of ketosis, follow-up management, and eventual discontinuation of the diet.

KEY WORDS: Ketogenic diet, Clinical management, Drug-resistant epilepsy.

The ketogenic diet (KD) is a nonpharmacologic treatment for childhood epilepsy not amenable to drugs (Stafstrom & Rho, 2004; Freeman et al., 2007) that mimics the biochemical response to starvation, when ketone bodies, rather then glucose, become the main fuel for the brain energy demand. In the past decade, interest in ketogenic diet spread worldwide (Kossoff & McGrogan, 2005; Lord & Magrath, 2010; Neal & Cross, 2010). At present, two works based on national research, one in Germany (Klepper et al., 2004) and one in the United States (Kossoff et al., 2008b) provide international guidelines to ensure a correct management of the KD. Our Italian collaborative study group was set up to create a consensus statement regarding the clinical management of the KD. The aim of the study is to establish more standardized protocols and management recommendations for Italian groups of child neuropsychiatrist, clinical nutritionists, and dietitians. The main suggestions concern patient selection, pre-KD counseling, setting and enforcement of dietary induction of ketosis, follow-up management, and eventual KD discontinuation.

Address correspondence to Pierangelo Veggiotti, Department of Child Neurology and Psychiatry, Fondazione IRCCS Istituto Neurologico C. Mondino, Pavia, Italy. E-mail: pveggiot@unipv.it

Consensus Recommendations

Patient selection

The two main indications (Table 1) to the ketogenic diet are glucose transporter protein 1 (GLUT-1) deficiency syndrome (Klepper & Leiendecker, 2007; Pons et al., 2010) and pyruvate dehydrogenase deficiency (PDHD) (Wexler et al., 1997). In both conditions the enzymatic defect causes a disorder of brain energy metabolism. The KD is the treatment of choice because the brain can use ketones as an alternative energy source, bypassing the obstacle in physiologic metabolism. GLUT-1 deficiency syndrome is an inborn error of glucose transport across the blood–brain barrier, characterized by a variable combination of seizures, development delay, acquired microcephaly, spasticity, and a complex movement disorder (Leen et al., 2010). The KD should be considered as a first-line therapy for this disease (Wang et al., 2009; Veggiotti et al., 2010). PDHD is a severe mitochondrial disease where pyruvate cannot be metabolized into acetyl-CoA

(Wexler et al., 1997; McWilliam et al., 2010; Barnerias et al., 2010). The KD is particularly useful for control of severe lactic acidosis in patients with this disorder.

Some cases of positive response to the diet are described in metabolic disorders such as phosphofructokinase deficiency (Swoboda et al., 1997), glycogenosis type V (Busch et al., 2005), and mitochondrial respiratory chain complex disorders (Kang et al., 2007a). In patients with medically refractory epilepsy or severe intolerance to antiepileptic drugs (AEDs), the KD is an important, potentially efficacious alternative. Some evidence indicates that patients with severe myoclonic epilepsy of infancy (or Dravet syndrome) (Caraballo et al., 2005, 2011) and myoclonic–astatic epilepsy may respond positively to the diet (Caraballo et al., 2006). Several retrospective studies reported that 60–75% of children with refractory seizures obtained a >50% decrease in their seizures (Kinsman et al., 1992; Freeman et al., 1998; Casey et al., 1999; Vining, 1999; Katyal et al., 2000; Coppola et al., 2002; Kossoff & McGrogan, 2005; Henderson et al., 2006; Freeman et al., 2007; Coppola et al., 2010; Lefevre & Aronson, 2010). The KD should be strongly considered in a child who failed two to three anticonvulsant therapies, regardless of age, and particularly in those with symptomatic generalized epilepsies.

The KD was shown to be particularly effective in infantile spasm (Hong et al., 2010), even before trying any anticonvulsant or steroid (Kossoff et al., 2008a,b; Kossoff, 2010). Furthermore, children receiving either concurrent vagus nerve stimulation or zonisamide may show preferential benefit when the KD is started (Kossoff et al., 2007b; Morrison et al., 2009). On the contrary children with partial seizures tend to have a worse response to the KD (Stainman et al., 2007). Clinical trials are currently ongoing on patients with Alzheimer disease, amyotrophic lateral sclerosis, migraine, and brain tumors (Van der Auwera et al., 2005; Zhao et al., 2006; Seyfried et al., 2008, 2009).

KD is contraindicated in several specific inborn errors of metabolism that could lead to a severe metabolic crisis. These metabolic diseases should, therefore, be ruled out before starting the diet. Patients with a disorder of fat metabolism might develop a severe worsening of the disease under KD. Therefore, before initiating the KD, children must be screened for disorders of fatty acid transport and oxidation (Kossoff et al., 2008a,b). An inborn metabolic error at any point along the pathway of fatty acid transportation by carnitine can lead to a devastating catabolic crisis (i.e., coma, death) during fasting or the KD. Deficiency of pyruvate carboxylase, a mitochondrial enzyme that catalyzes the conversion of pyruvate to oxaloacetate, can impair tricarboxylic acid cycle function and energy production in patients on the KD. The diet can exacerbate acute intermittent porphyria.

Table 1. Main indications for dietary therapy

Metabolic disorders
Glucose transporter protein 1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Mitochondrial respiratory chain complex disorders
Epilepsy
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Medically refractory epilepsy
Severe intolerance to AEDs

Pre–ketogenic diet counseling

Several important prerequisites assessing the patient eligibility for the KD ensure both safety and maximization of chances of success (Table 2). Pediatric, neurologic, and nutritional consults before the introduction of KD are recommended. An evaluation of epilepsy is needed to identify seizure type(s), frequency, and etiology; the clinician should also review all past and current AEDs. A wakefulness and a sleep electroencephalography (EEG) (24 h EEG if needed) and brain magnetic resonance imaging (MRI) will be useful to identify those patients who are susceptible to surgical treatment. A cognitive or developmental assessment is needed to evaluate the neuropsychological outcome. As part of diagnostic work-up in progressive epileptic encephalopathies, a full serum and urine metabolic evaluation (urine organic acids, serum amino acids, ammonium, lactic acid, serum acylcarnitine profile) should be performed if no clear etiology for the child's epilepsy was identified.

Table 2. Pre-KD evaluation

Neurologic evaluation
Etiology
Seizure type
Seizure frequency
AEDs and other medication review
EEG/Holter EEG
MRI
Cognitive/development assessment
Full serum and urine metabolic evaluation
Pediatric evaluation
ECG if history of heart disease
Abdomen ultrasound
Laboratory analysis
Nutritional evaluation
Baseline weight, height, and ideal weight for stature
Body mass index (BMI)
Skinfold thickness measurement
Dietary history
Bioelectrical impedance analysis
Indirect calorimetry[a]
Dual energy x-ray absorptiometry (DEXA)[a]
Counseling

[a]If these last two tests are not available, the use of predictive equations of basal metabolic rate and wrist x-ray could be performed

Heart and abdominal ultrasound is important to rule out metabolic disorders unsuited to the diet and to point out any complication (presence of kidney stones, dyslipidemia, liver disease, gastroesophageal reflux, and cardiomyopathy). Laboratory evaluation before starting the KD should include complete blood count with platelets, serum, liver, and kidney tests (including albumin, prealbumin, ammonium, AST, ALT, ALP, γGT, total and direct bilirubin, blood urea, nitrogen, and creatinine), a fasting lipid profile (triglycerides, total cholesterol, high-density lipoproteins, low-density lipoproteins, and atherogenic index), blood sugar level, electrolytes (paying particular attention to serum bicarbonate, total protein, calcium, zinc, selenium, magnesium, and phosphate), blood gas analysis, parathyroid hormone and vitamin D, osteocalcin (if osteopenia), urinalysis and 24 h urine calcium and creatinine, and antiepileptic drug levels (if applicable).

Dietetic and nutritional evaluation consists of measurement of baseline weight, height, body mass index (BMI) and ideal weight for stature, skinfold thickness measurement, bioelectrical impedance analysis, indirect calorimetry (basal metabolism evaluation), and dual energy x-ray absorptiometry (DEXA; if the latter two tests are unavailable, the use of predictive equations of basal metabolic rate and wrist x-ray should be performed). A dietary history (7-day food record, food preferences, allergies, aversions, and intolerances) is needed.

All these investigations are strongly recommended in first-time patient evaluation; during the patient follow-up, tests should be chosen based on clinical course.

Before starting the diet, it is also crucial to discuss psychosocial issues. The physician should ensure that parents or caregivers understand their involvement in administering the KD to their child, specifically the importance of strict adherence to the diet, avoidance of carbohydrates, need for multivitamin and mineral supplementation, and awareness of potential adverse effects (Kossoff et al., 2008a,b).

Patients' families are often worried about how much time is needed to obtain therapeutic success with the KD; the clinician is advised to discuss this choice with the child's parents and to indicate a minimum of 3 months.

Setting and enforcement of dietary induction of ketosis

The traditional method of initiating KD involves a period of fasting, with no carbohydrate-containing fluids and, periodically monitoring serum glucose (Freeman et al., 2006). Duration of fasting varies from 12–48 h, depending on the time required to achieving adequate ketosis; after reaching a level of beta-hydroxybutyrate in the blood >2 mM, food may be progressively administered. The caloric contribution of meals is increased daily in one-third caloric intervals to reach full calories meals; an adequate level of beta-hydroxybutyrate is considered to be 2–5 mM, 7 days after the diet. Fasting may result in hypoglycemia, acidosis, nausea, vomiting, dehydration, and lethargy; therefore, instituting the traditional KD protocol in the hospital is indicated to prevent any possible complication.

Nowadays it's evident that fasting may be appropriate when it's necessary to obtain a quicker response to the diet (Freeman & Vining, 1999; Kossoff et al., 2008b), but it is not necessary for long-term efficacy. Retrospective (Kim et al., 2004) and prospective studies indicate that gradual initiation protocols offer the same seizure control at 3 months compared to traditional KD protocol, together with significant lower frequency and severity of initiation related side effects (Bergqvist et al., 2005).

The KD can also be started in outpatients, in selected cases, following a standardized procedure to screen neurologic, general pediatric, metabolic, and nutritional conditions before administration. Potential advantages of gradually starting the diet outside the hospital include reduced stress for the child, lower risk of hypoglycemia and dehydration, reduced number of laboratory analysis, and reduced costs.

The optimal way to administer the KD depends on the type of feeding. Children who have normal oral feeding can get the diet in the food that is prepared following specific dietary indications, whereas enterally (including gastrostomy and jejunostomy) fed children can use a formula-based KD, which is generally simpler for dietitians to calculate; the formula is also often used as add on in children who are orally fed.

Classic KD is calculated in grams of fat to grams of proteins plus carbohydrates. The most common ratio is 4 g of fat to 1 g of protein plus carbohydrate (described as "4:1"). This means that 90% of the energy comes from fats and 10% from proteins and carbohydrates combined. Sometimes it is necessary to provide the KD at a lower ratio to increase intake of proteins or carbohydrates (often "3:1"). There is some evidence that a 4:1 ratio, when used at the start, may be more advantageous for the first 3 months (Seo et al., 2007). During the first month, calories are typically restricted to 75% of the daily recommendations for age, to promote ketosis. But this reduction is not necessary; underweight children should not follow this protocol and all children should increase calories gradually over time to the regular recommendations for age.

Similarly, fluid restriction to 90% is based on consolidated habits rather than on scientific evidence. We do not suggest fluid restriction for children on KD; the fluid administration (noncaloric fluids) is individualized (1–10 kg need 80 ml/kg; 10–20 kg need 800 ml + 40 ml/kg; >20 kg need 1,200 ml + 20 ml/kg) and increased contextually to the child's level of activity or adjusted for climate; in infants fluids should be increased to 100 ml per kilogram of body weight.

The KD may also be easily administered to enterally fed children. Prescription of a formula-based KD is generally

Table 3. Transition from enteral diet in Ketocal (4 days)

Stage	Days	Enteral diet (%)	Ketocal (%)
1	1–2	Energy 75	Energy 25
2	1–2	Energy 50	Energy 50
3	1–2	Energy 25	Energy 75
4		Energy 0	Energy 100

needed in the case of coma, low caloric intake by mouth due to conditions such as respiratory and gastrointestinal problems, severe neurologic impairment, failure to thrive, poor compliance with traditional KD, and for children younger than 12 months of age. The transition from an enteral diet to KD should be gradual (Table 3). The formula-based KD is easily administered and is used also in mouth-fed children to adjust caloric intake and substitute regular food in special circumstances (on a journey, etc.). To prepare a formula-based KD, in Europe a commercial product is currently available. KetoCal (for North America: Nutricia, Rockville, MD, U.S.A. and for Europe: SHS International, Liverpool, U.K.) is a milk protein-based, powdered formula that, added to water, provides either a 3:1 or 4:1 KD.

In the past few years, modified dietary approaches have been developed for the treatment of epilepsy, including the modified Atkins diet (Kossoff et al., 2006, 2007b; Kang et al., 2007b), the MCT diet (Liu, 2008; Neal et al., 2008) and the low-glycemic diet (Pfeifer et al., 2008). Unlike the classic KD, the modified Atkins diet is started without hospitalization and does not require precise weighing of food ingredients and portions. The daily carbohydrate consumption in the modified Atkins diet is 10 or 20 g (Kossoff et al., 2007b). However, there are no limitations in protein, fluids, and calories. This diet is easier to administer in adolescents and adults than in children.

Because of limited food choice, the classic KD is also deficient in minerals and vitamins, and needs to be supplemented with sugar-free products. Inadequate calcium intake and limited sun exposure can impair bone mineralization in children at risk of osteopenia and osteoporosis due to long-term antiepileptic drug (AED) therapy. Therefore, both vitamin D and calcium should be supplemented (Bergqvist et al., 2007). Additional supplementation (zinc, selenium, magnesium, phosphorus, and so on) using standard multivitamin products is suggested. Carnitine oral supplementation (50 mg/kg/die) is needed if laboratory levels are low (Coppola et al., 2006) or children exhibit symptoms indicating hypocarnitinemia such as generalized weakness, excessive fatigue, and decreased muscle strength.

Table 4. Follow-up KD management

- Neurologic assessment
  - Neurologic evaluation (at 1–3–6–12 months)
  - Electroencephalography (at 1–3–6–12 months)
  - Review efficacy of the diet
  - Cognitive/development evaluation (at 6–12 months)
- Pediatric assessment
  - Electrocardiography (every 6 months)
  - Abdominal echo (every 6 months)
  - Laboratory evaluation (at 1–3–6–12 months)
  - Complete blood count with plates
  - Serum liver and kidney tests
  - Blood sugar level
  - Electrolytes
  - Blood gas analysis
  - Laboratory evaluation (at 3–6–12 months)
  - Fasting lipid profile
  - Parathormone and vitamin D
  - Osteocalcin (if osteopenia)
  - Urinalysis and 24 h urine calcium and creatinine (only if previously altered)
  - Anticonvulsant drug levels
- Nutritional assessment
  - Assess compliance to therapy
  - Height and body mass index (BMI)
  - Skinfold thickness measurements
  - Bioelectrical impedance analysis
  - Indirect calorimetry (each 3 months)
  - Dual energy x-ray absorptiometry or wrist x-ray (every 6–12 months)
  - Review appropriateness of diet prescription (calories, protein, and fluid)
  - Review vitamin and mineral supplementation

Follow-up management

Follow-up of children receiving KD includes regular neurologic, nutritional, and pediatric evaluations (Table 4). The child should be examined by the neurologist initially at the 8th and 15th day after hospital discharge and EEG performed (if the child is is younger than 1 year of age or an epileptic encephalopathy is present) or at least after 1, 3, 6, 9, and 12 months in the first year of treatment. Cognitive and developmental assessment should be performed 6 and 12 months after introducing the KD. Electrocardiography (ECG), heart ultrasound and an abdominal echo should be performed every 6 months.

The laboratory evaluation at 1, 3, 6, and 12 months after introduction of the KD includes complete blood count with platelets, serum, liver and kidney tests (including albumin, prealbumin, ammonium, AST, ALT, ALP, Gamma-GT, total and direct bilirubin, blood urea, nitrogen, and creatinine), glycemia, electrolytes (especially serum bicarbonate, total protein, calcium, zinc, selenium, magnesium, and phosphate) and blood gas analysis.

At 3, 6, and 12 months, the following evaluations should be performed: fasting lipid profile (triglycerides, total cholesterol, HDL, LDL), parathyroid hormone and vitamin D, osteocalcin (if osteopenia), urinalysis, 24 h urine calcium and creatinine (only if previously altered), and AED levels (if applicable).

The dietetic and nutritional evaluation consists of a review of diet and compliance, the measurement of weight, height, BMI, skinfold thickness, and bioelectrical impedance analysis at each visit; indirect calorimetry (basal metabolism evaluation) every 3 months, DEXA, or wrist x-ray every 6–12 months.

At home, routine urine ketosis evaluation should be performed by parents twice per day (morning and evening) at least in the first 3 months, and then once a week; the optimal level of ketones in the urine is 8–16 mM evaluated by keto-diastix (Bayer Health Care, Milano, Italy). Serum β-hydroxybutyrate (BHB) should be measured every 12 h until its stabilization, and then regular controls should be performed at 1, 3, 6, 12, and 24 months or in case of symptoms referable to hyperketosis or worsening of seizures. It seems that BHB is better correlated to seizure reduction than are ketones in the urine. Therefore, it is preferable to use BHB to monitor the KD even if BHB is measured less frequently than urinary ketones (Van Delft et al., 2010). Serum glycemia should be evaluated every 12 h (every 6 h in the first 48 h if the child is aged <12 months); optimal level of serum glycemia is 2.5–5 mM.

Glycemic values <2.5 mM and/or ketones values >6.5 mM, if symptomatic (sweating, palor, and tremor), require immediate oral administration of glucose, maltodextrin, or fruit juice; in case of impaired alertness, administration of intravenous glucose is essential.

Growth parameters such as weight and height should be regularly controlled during the first year of the KD, in order to monitor appropriate weight gain for age and length; infants younger than 2 years of age should be monitored more frequently (almost weekly) to prevent growth disturbance (Vining et al., 2002). If a child is overly hungry or refuses his meal, calorie contribution should be adjusted accordingly.

As in all medical therapies, side effects can occur during the diet and neurologists, clinical nutritionists, and dietitians need to be alerted (Ballaban-Gil et al., 1998; Wheless, 2001). However, the risk of serious adverse events is low. Metabolic abnormalities include hypoproteinemia that causes muscular mass loss or alteration in bone metabolism; hyperlipidemia or hypercholesterolemia, reported in 14–59% of children on KD (Chesney et al., 1999; Kwiterovich et al., 2003; Kang et al., 2004) that can cause atherosclerosis; hypocalcemia (2%) that can worsen a preexisting osteopenia or osteoporosis; potassium or selenium deficit that can cause cardiac abnormalities; hyperuricemia (2–26%), hypomagnesemia (5%), decreased amino acid levels, and acidosis (2–5%) (Schwartz et al.,1989; Chesney et al., 1999; Kang et al., 2004). Metabolic abnormalities can be prevented by careful monitoring.

Gastrointestinal symptoms including vomiting, constipation, diarrhea, and abdominal pain occur in 12–50% of children on the KD (Kang et al., 2004); renal calculi occur in 3–7% (Furth et al., 2000; Kossoff et al., 2002; Sampath et al., 2007) making regular monitoring necessary (Choi et al., 2010). Potassium citrate supplementation is warranted to reduce the incidence of kidney stones (McNally et al., 2009).

Long-term complications in children treated with KD for >2 years have been reported (Groesbeck et al., 2006). In the small population studies, the higher risk was referred to bone fractures, kidney stones, and decreased growth. KD discontinuation depends on the patient's response to the diet; even if apparently ineffective, the diet must be maintained for at least 3 months (Freeman et al., 2006) before considering discontinuation. In children with >50% seizure response, the KD is often discontinued after approximately 2 years; however, in children in whom seizure control is nearly complete and side effects are low, the diet can be prolonged up to 6–12 years (Groesbeck et al., 2006). A longer diet duration is needed for children with GLUT-1 and PDHD deficiency syndromes. No information is available about the maximum duration of the KD, but seizure-free patients on the diet for >10 years have been reported. A recent study revaluated the long-term outcomes in safety and efficacy of KD after its discontinuation, providing reassuring results with regard to seizures and adverse effects (Patel et al., 2010).

In assessing the effectiveness of the KD, rate of seizure reduction should not be the only parameter (Beniczky et al., 2010), duration of improved seizure control and the possible global improvement of patient well being are also important.

Acknowledgment

This work was obtained from a Consensus established in Verona on November 2009.

Disclosure

Drs. Veggiotti, Tagliabue, Coppola, and Guerrini and Dalla Bernardina have received support for research and/or consulting from Nutricia. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Ballaban-Gil K, Callahan C, O'Dell C, Pappo M, Moshe S, Shinnar S. (1998) Complications of the ketogenic diet. *Epilepsia* 39:744–748.

Barnerias C, Saudubray JM, Touati G, De Lonlay P, Dulac O, Ponsot G, Marsac C, Brivet M, Desguerre I. (2010) Pyruvate dehydrogenase complex deficiency: four neurological phenotypes with differing pathogenesis. *Dev Med Child Neurol* 52:e1–e9.

Beniczky S, Jose Miranda M, Alving J, Heber Povlsen J, Wolf P. (2010) Effectiveness of the ketogenic diet in a broad range of seizure types and EEG features for severe childhood epilepsies. *Acta Neurol Scand* 121:58–62.

Bergqvist AG, Schall JI, Gallagher PR, Cnaan A, Stallings VA. (2005) Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. *Epilepsia* 46:1810–1819.

Bergqvist AG, Schall JI, Stallings VA. (2007) Vitamin D status in children with intractable epilepsy, and impact of the ketogenic diet. *Epilepsia* 48:66–71.

Busch V, Gempel K, Hack A, Muller K, Vorgerd M, Lochmuller H, Baumeister FA. (2005) Treatment of glycogenosis type V with ketogenic diet. *Ann Neurol* 58:341.

Caraballo RH, Cersosimo RO, Saks D, Cresta A, Escobal N, Fejerman N. (2005) Ketogenic diet in patients with Dravet Syndrome. *Epilepsia* 46:1539–1544.

Caraballo RH, Cersosimo RO, Saks D, Cresta A, Escobal N, Fejerman N. (2006) Ketogenic diet in patients with myoclonic astatic epilepsy. *Epileptic Disord* 8:151–155.

Caraballo RH. (2011) Nonpharmacologic treatments of Dravet Syndrome: Focus on the ketogenic diet. *Epilepsia* 52(Suppl. 2):79–82.

Casey JC, McGrogan J, Pillas D, Pyzik P, Freeman J, Vining EP. (1999) The implementation and maintenance of the Ketogenic Diet in children. *J Neurosci Nurs* 31:294–302.

Chesney D, Brouhard BH, Wyllie E, Powaski K. (1999) Biochemical abnormalities of the ketogenic diet in children. *Clin Pediatr* 38:107–109.

Choi JN, Song JE, Shin JI, Kim HD, Kim MJ, Lee JS. (2010) Renal stone associated with the ketogenic diet in a 5-year old girl with intractable epilepsy. *Yonsei Med J* 51:457–459.

Coppola G, Veggiotti P, Cusmai R, Bertoli S, Cardinali S, Dionisi-Vici C, Elia M, Lispi ML, Sarnelli C, Tagliabue A, Toraldo C, Pascotto A. (2002) The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience. *Epilepsy Res* 48:221–227.

Coppola G, Epifanio G, Auricchio G, Federico RR, Resicato G, Pascotto A. (2006) Plasma free carnitine in epilepsy children, adolescents and young adults treated with old and new antiepileptic drugs with or without ketogenic diet. *Brain Dev* 28:358–365.

Coppola G, Verrotti A, Ammendola E, Operto FF, Corte RD, Signoriello G, Pascotto A. (2010) Ketogenic diet for the treatment of catastrophic epileptic encephalopathies in childhood. *Eur J Paediatr Neurol* 14:229–234.

Freeman JM, Vining EPG. (1999) Seizures decrease rapidly after fasting: preliminary studies of the ketogenic diet. *Arch Pediatr Adolesc Med* 153:946–949.

Freeman JM, Vining EPG, Pillas DJ, Pyzik PL, Casey JC, Kelly MT. (1998) The efficacy of the ketogenic diet – 1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 102:1358–1363.

Freeman JM, Kossoff EH, Freeman JB, Kelly MT. (2006) *The ketogenic diet: a treatment for epilepsy in children and others*. 4th ed. Demos, New York.

Freeman JM, Kossoff EH, Hartman AL. (2007) The ketogenic diet: one decade later. *Pediatrics* 119:535–543.

Furth SL, Casey JC, Pyzik PL, Neu AM, Docimo SG, Vining EP, Freeman JM, Fivush BA. (2000) Risk factors for urolithiasis in children on the ketogenic diet. *Pediatric Nephrol* 15:125–128.

Groesbeck DK, Bluml RM, Kossoff EH. (2006) Long-term use of the ketogenic diet in the treatment of epilepsy. *Dev Med Child Neurol* 48:978–981.

Henderson CB, Filloux FM, Alder SC, Lyon JL, Caplin DA. (2006) Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. *J Child Neurol* 21:193–198.

Hong AM, Turner Z, Hamdy RF, Kossoff EH. (2010) Infantile spasm treated with the ketogenic diet: Prospective single-center experience in 104 consecutive infants. *Epilepsia* 51:1403–1407.

Kang HC, da Chung E, Kim DW, Kim HD. (2004) Early and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia* 45:1116–1123.

Kang HC, Lee YM, Kim HD, Lee JS, Slama A. (2007a) Safe and effective use of the ketogenic diet in children with epilepsy and mitochondrial respiratory chain complex defects. *Epilepsia* 48:82–88.

Kang HC, Lee HS, You SJ, Kang DC, Ko TS, Kim HD. (2007b) Use of a modified Atkins diet in intractable childhood epilepsy. *Epilepsia* 48:182–186.

Katyal NG, Koehler AN, McGhee B, Foley CM, Crumrine PK. (2000) The ketogenic diet in refractory epilepsy: the experience of Children's Hospital of Pittsburgh. *Clin Pediatr (Phila)* 39:153–159.

Kim DW, Kang HC, Park JC, Kim HD. (2004) Benefits of the nonfasting ketogenic diet compared with the initial fasting ketogenic diet. *Pediatrics* 114:1627–1630.

Kinsman SL, Vining EP, Quaskey SA, Mellits D, Freeman JM. (1992) Efficacy of the ketogenic diet for intractable seizure disorders: review of 58 cases. *Epilepsia* 33:1132–1136.

Klepper J, Leiendecker B. (2007) GLUT1 deficiency syndrome – 2007 update. *Dev Med Child Neurol* 49:707–716.

Klepper J, Leiendecker B, Riemann E, Baumeister FA. (2004) The ketogenic diet in German-speaking countries: update 2003. *Klin Padiatr* 216:277–285.

Kossoff EH. (2010) Infantile spasms. *Neurologist* 16:69–75.

Kossoff EH, McGrogan JR. (2005) Worldwide use of the ketogenic diet. *Epilepsia* 46:280–289.

Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EPG. (2002) Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. *Epilepsia* 43:1168–1171.

Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. (2006) A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia* 47:421–424.

Kossoff EH, Pyzik PL, Rubenstein JE, Bergqvist AG, Buchhalter JR, Donner EJ, Nordli DR Jr, Wheless JW. (2007a) Combined ketogenic diet and vagus nerve stimulation: rational polytherapy? *Epilepsia* 48:77–81.

Kossoff EH, Turner Z, Bluml RM, Pyzik PL, Vining EP. (2007b) A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. *Epilepsy Behav* 10:432–436.

Kossoff EH, Hedderick EF, Turner Z, Freeman JM. (2008a) A case–control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. *Epilepsia* 49:1504–1509.

Kossoff EH, Laux LC, Blackford R, Morrison PF, Pyzik PL, Turner Z, Nordli DL Jr. (2008b) When do seizures improve with the ketogenic diet? *Epilepsia* 49:329–333.

Kwiterovich PO Jr, Vining EP, Pyzik P, Skolasky R Jr, Freeman JM. (2003) Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. *JAMA* 290:912–920.

Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, van Engelen BG, Wevers RA, Arthur T, Bahi-Buisson N, Ballhausen D, Bekhof J, van Bogaert P, Carrilho I, Chabrol B, Champion MP, Coldwell J, Clayton P, Donner E, Evangeliou A, Ebinger F, Farrell K, Fersyth RJ, de Goede CG, Gross S, Grunewald S, Holthausen H, Jayawant S, Lachlan K, Laugel V, Leppig K, Lim MJ, Mancini G, Marina AD, Martorell L, McMenamin J, Meuwissen ME, Mundy H, Nilsson NO, Panzer A, Poll-The BT, Rauscher C, Rouselle CM, Sandvig I, Scheffner T, Sheridan E, Simpson N, Sykora P, Tomlinson R, Trounce J, Webb D, Weschke B, Scheffer H, Willemsen MA. (2010) Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. *Brain* 133(Pt 3):655–670.

Lefevre F, Aronson N. (2010) Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. *Pediatrics* 105:E46.

Liu YC. (2008) Medium-chain triglyceride ketogenic therapy. *Epilepsia* 49(suppl 8):33–36.

Lord K, Magrath G. (2010) Use of the ketogenic diet and dietary practices in the UK. *J Hum Nutr Diet* 23:126–132.

McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff E. (2009) Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. *Pediatrics* 124:e300–e304.

McWilliam CA, Ridout CK, Brown RM, McWilliam RC, Tolmie J, Brown GK. (2010) Pyruvate dehydrogenase E2 deficiency: a potentially treatable cause of episodic dystonia. *Eur J Paediatr Neurol* 14:349–353.

Morrison PF, Pyzik PL, Hamdy R, Hartman AL, Kossoff EH. (2009) The influence of concurrent anticonvulsants on the efficacy of the ketogenic diet. *Epilepsia* 50:1999–2001.

Neal EG, Cross JH. (2010) Efficacy of dietary treatments for epilepsy. *J Hum Nutr Diet* 23:113–119.

Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross H. (2008) A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia* 49:1–9.

Patel A, Pyzik PL, Turner Z, Rubenstein JE, Kossoff EH. (2010) NLong-term outcomes of children treated with the ketogenic diet in the past. *Epilepsia* 51:1277–1282.

Pfeifer HH, Lyczkowski DA, Thiele EA. (2008) Low glycemic index treatment: implementation and new insights into efficacy. *Epilepsia* 49(suppl 8):42–45.

Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. (2010) The spectrum of movement disorders in Glut-1 deficiency. *Mov Disord* 25:275–281.

Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EPG. (2007) Kidney stones and the ketogenic diet: risk factors and prevention. *J Child Neurol* 22:375–378.

Schwartz RH, Eaton J, Bower BD, Aynsley-Green A. (1989) Ketogenic diets in the treatment of epilepsy: short-term clinical effects. *Dev Med Child Neurol* 31:145–151.

Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. (2007) Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios–comparison of 3:1 with 4:1 diet. *Epilepsia* 48:801–805.

Seyfried TN, Kiebish M, Mukherjee P, Marsh J. (2008) Targeting energy metabolism in brain cancer with calorically restricted ketogenic diets. *Epilepsia* 49(suppl8):114–116. Review.

Seyfried BT, Kiebish M, Marsh J, Mukherjee P. (2009) Targeting energy metabolism in brain cancer through calorie restriction and the ketogenic diet. *J Cancer Res Ther* 5(Suppl. 1):S7–S15. Review.

Stafstrom CE, Rho JM. (2004) *Epilepsy and the ketogenic diet.* Humana Press, Totawa.

Stainman RS, Turner Z, Rubenstein JE, Kossoff EH. (2007) Decreased relative efficacy of the ketogenic diet for children with surgically approachable epilepsy. *Seizure* 16:615–619.

Swoboda KJ, Specht L, Jones HR, Shapiro F, DiMauro S, Korson M. (1997) Infantile phosphofructokinase deficiency with arthrogryposis: clinical benefit of a ketogenic diet. *J Pediatr* 131:932–934.

van Delft R, Lambrechts D, Verschuure P, Hulsman J, Majoie M. (2010) Blood beta-hydroxybutyrate correlates better with seizure reduction due to ketogenic diet than do ketones in the urine. *Seizure* 19:36–39.

Van der Auwera I, Wera S, Van Leuven F, Henderson ST. (2005) A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutr Metab (Lond)* 2:28.

Veggiotti P, Teutonico F, Alfei E, Nardocci N, Zorzi G, Tagliabue A, De Giorgis V, Balottin U. (2010) Glucose transporter type 1 deficiency: ketogenic diet in three patients with atypical phenotype. *Brain Dev* 32:404–408.

Vining EP. (1999) Clinical efficacy of the ketogenic diet. *Epilepsy Res* 37:181–190. Review.

Vining EP, Pyzik P, McGrogan J, Hladky H, Anand A, Kriegler S, Freeman JM. (2002) Growth of children on the ketogenic diet. *Dev Med Child Neurol* 44:796–802.

Wang D, Pascual JM, De Vivo D. (2009) Glucose transporter type 1 deficiency syndrome. In: Pagon RA, Bird TC, Dolan CR, Stephens K (Eds) *GeneReviews* [internet]. Seattle (WA). University of Washington, Seattle, 1993–2002 Jul 30 [updated 2009 Jul 7] Available from: www.genereviews.org [Accessed October 20, 2010].

Wexler ID, Hemalatha SG, McConnell J, Buist NR, Dahl HH, Berry SA, Cederbaum SD, Patel MS, Kerr DS. (1997) Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations. *Neurology* 49:1655–1661.

Wheless JW. (2001) The ketogenic diet: an effective medical therapy with side effects. *J Child Neurol* 16:633–635.

Zhao Z, Lange DJ, Voustianiouk A, MacGrogan D, Ho L, Suh J, Humala N, Thiyagarajan M, Wang J, Pasinetti GM. (2006) A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. *BMC Neurosci* 7:29.