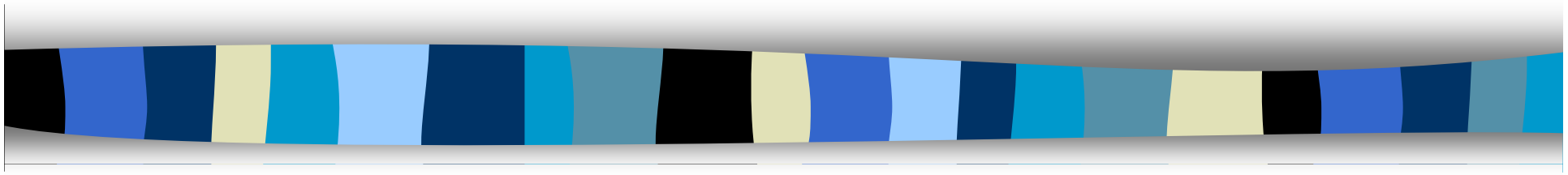
The ketogenic diet in pediatric neurology practice



- biochemical principles
- practical applications

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Some points from history

- 1921-1928: « The efficiency of fasting » and being free of seizures
- 1921-1970: the efficiency of ketogenic diet in 11 up to 60 % cases
- 1998: again interests for **epilepsy control**
- but yet not so much used
- arrival of new AED
- recent arrival of Ketocal
- recent promise in **brain oncology**

Main neurologic indications of ketogenic diets

- Epilepsy between 1 - 16 years with

Intractable seizure: >seizures/week although 2 AEDs

poor drugs tolerance

candidates for surgery

- neurometabolic disorders: Rett syndrome, GLUT1-DS, PDH deficiency, Leigh syndrome, P-fructokinase deficiency, ketotic hypoglycemia.
- Brain cancer

The glial-neuron metabolic unit

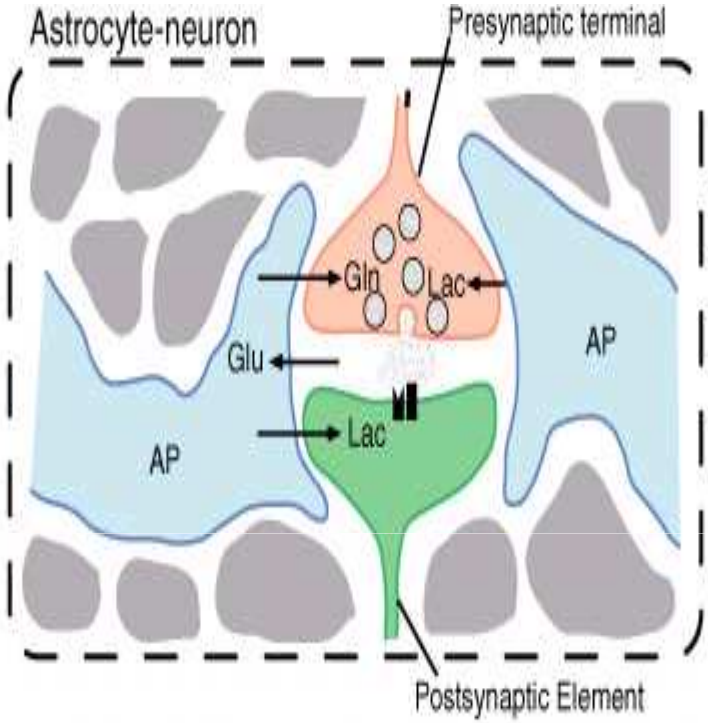

FIGURE 3.14 The astrocyte–neuron metabolic unit. Glutamatergic terminals and the astrocytic processes that surround them can be viewed as a highly specialized metabolic unit in which the activation signal (glutamate) is furnished by the neuron to the astrocyte, whereas the astrocyte provides the precursors needed to maintain the neurotransmitter pool (glutamine, lactate, alanine), as well as the energy substrate (lactate). AP, astrocyte process.

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The special astrocyte-neuron collaboration

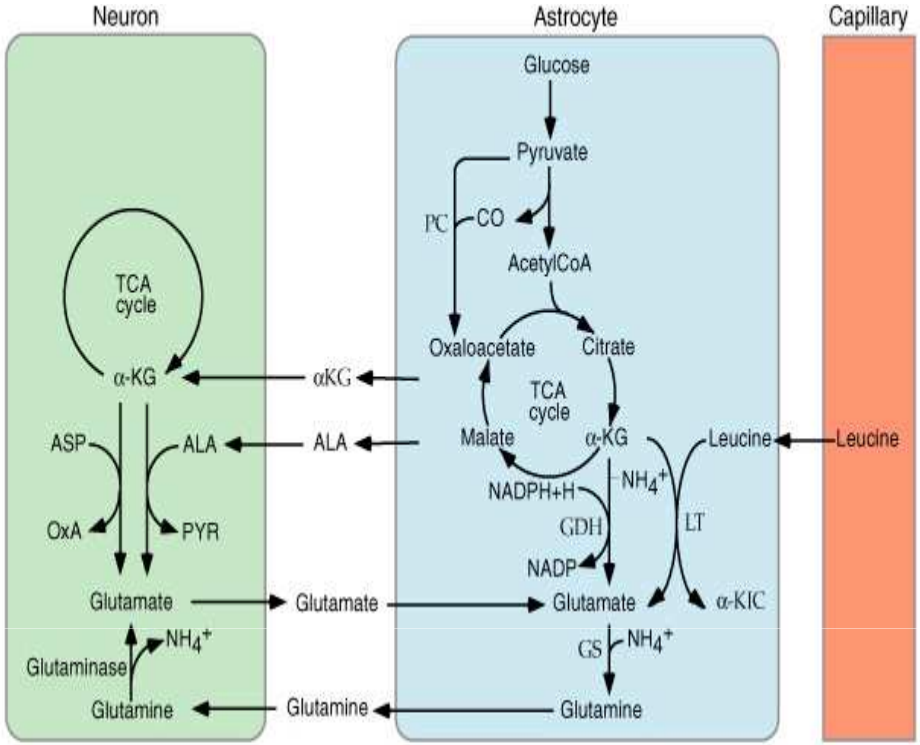

FIGURE 3.13 Metabolic intermediates are released by astrocytes to regenerate the glutamate neurotransmitter pool in neurons. Glutamine, formed from glutamate in a reaction catalyzed by glutamine synthase (GS), is released by astrocytes and taken up by neurons, which convert it into glutamate under the action of glutaminase. GS is an enzyme selectively localized in astrocytes. This metabolic cycle is referred to as the glutamate–glutamine shuttle. Other, quantitatively less important sources of neuronal glutamate are lactate, alanine, and α-ketoglutarate (α-KG). In astrocytes, glutamate is synthesized *de novo* from α-KG in a reaction catalyzed by glutamate dehydrogenase (GDH). The carbon backbone of glutamate is exported by astrocytes after conversion into glutamine under the action of GS; the conversion of leucine into α-ketoisocaproate (α-KIC), catalyzed by leucine transaminase (LT), provides the amino group for the synthesis of glutamine from glutamate. The carbons "lost" from the TCA cycle as α-KG is converted into glutamate are replenished by oxaloacetate (OxA) formed from pyruvate in a reaction catalyzed by pyruvate carboxylase (PC), another astrocyte-specific enzyme.

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Glucose transporters distribution in CNS

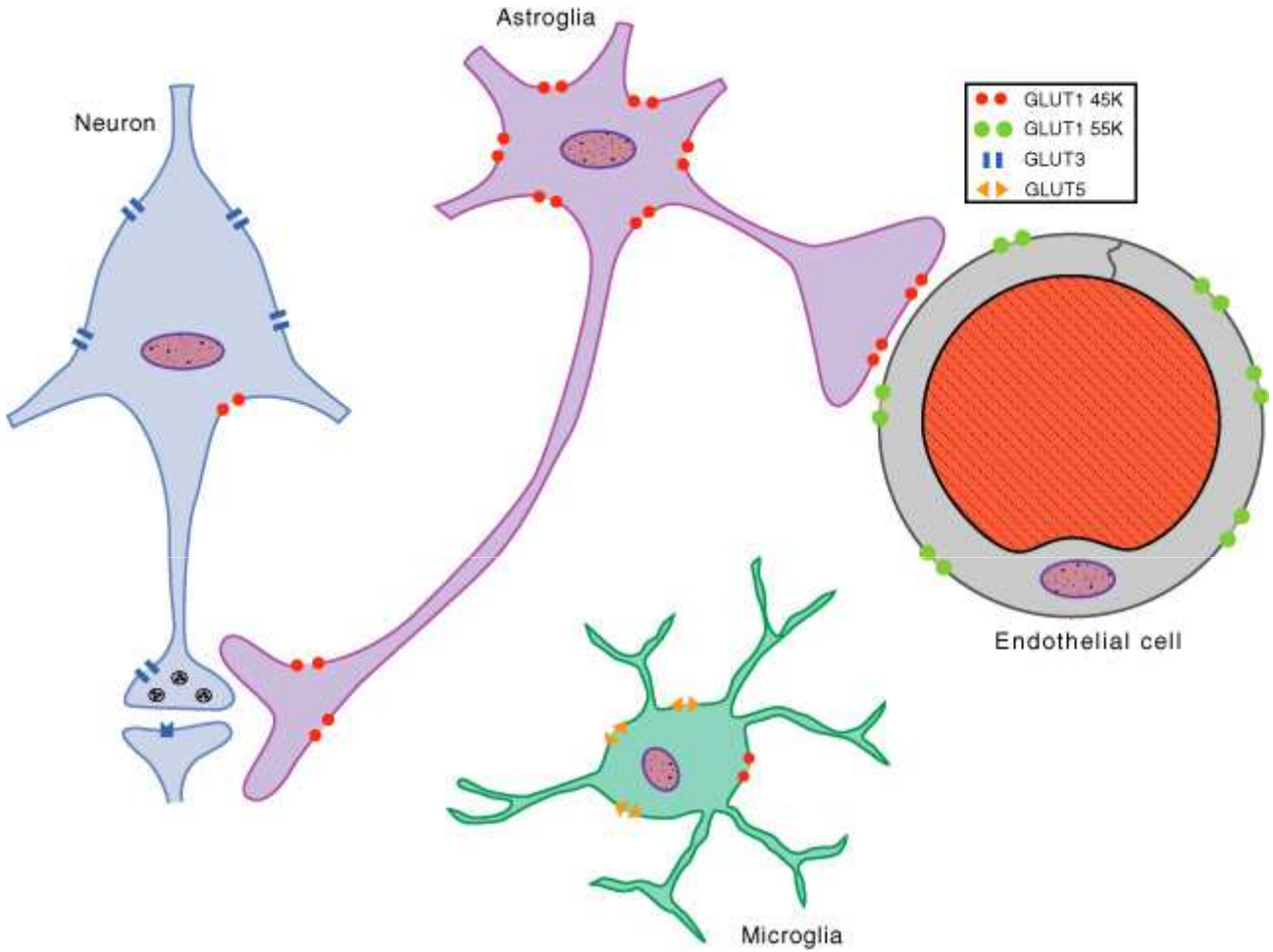

FIGURE 3.9 Cellular distribution of the principal glucose transporters in the nervous system.

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100 g of brain tissue

4 g neurons
40 g glia
10 ml CSF
4 ml blood
5 mg G /min
3 ml O2 /min

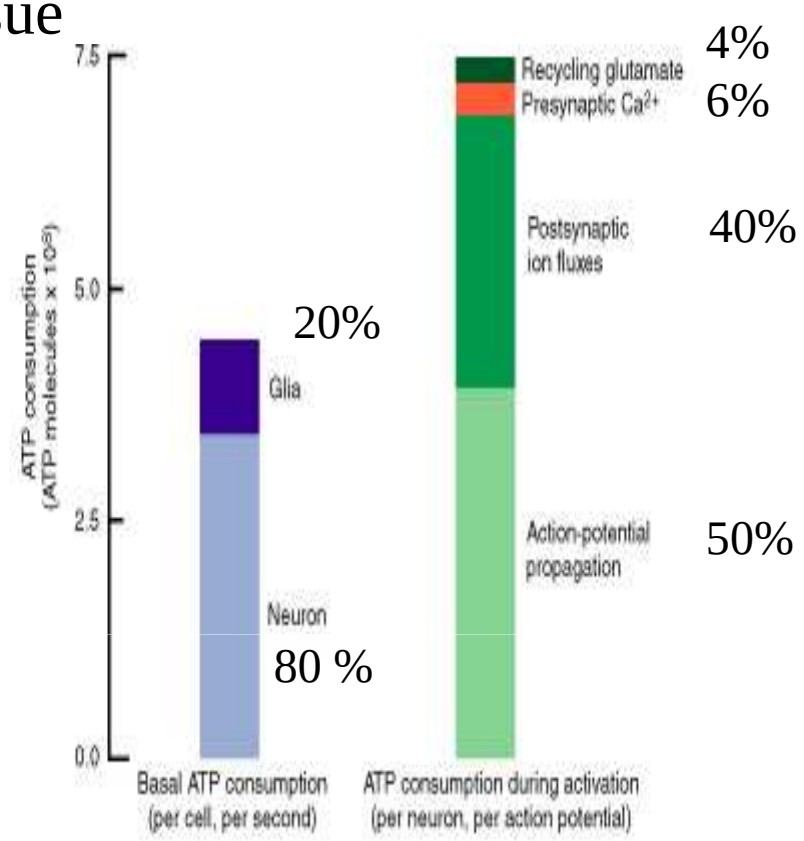

FIGURE 3.7 Energy budget for the rodent central cortex (Attwell and Laughlin, 2001). Relative rates of ATP consumption by resting neurons and glia (left). Relative cost of the various processes associated with a firing rate of 4 Hz for a glutamatergic pyramidal neuron. Modified from Laughlin and Attwell in Frackowiak et al. (2001).

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Glucose and energy in cells: cytoplasm and mitochondria

In a normal cell: G + O2 —(> 95 %)→ ATP + CO2 + H2O

Free radicals → coupled radicals

In a cell with mitochondrial impairement:

G + O2 → ATP + CO2 + lactic acid

hypoxia → Loss of energy and Electrolytes disturbances

reoxygenation → Free radicals

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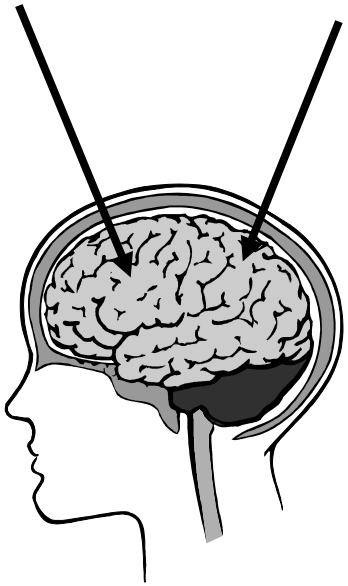
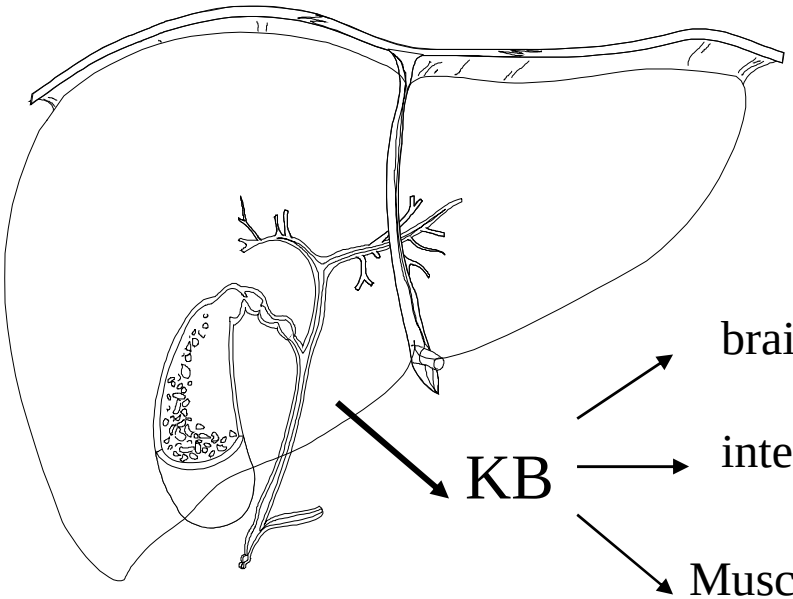
Time for shifting
main source of fuel:
3 weeks

Glucose - - - - KB

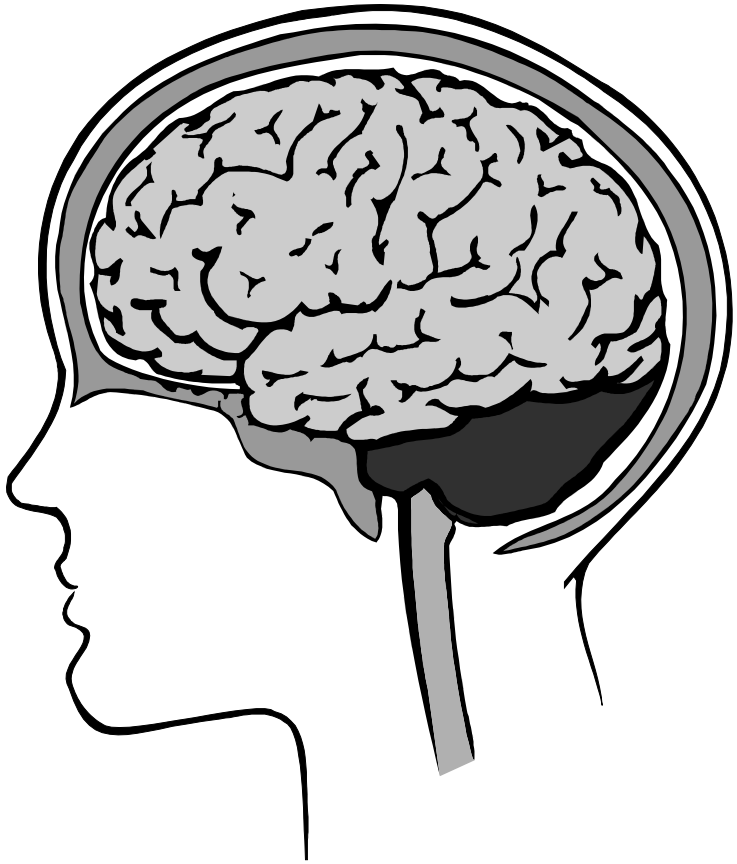


From Oral route or from adipose tissue

FFA



Mechanisms of action



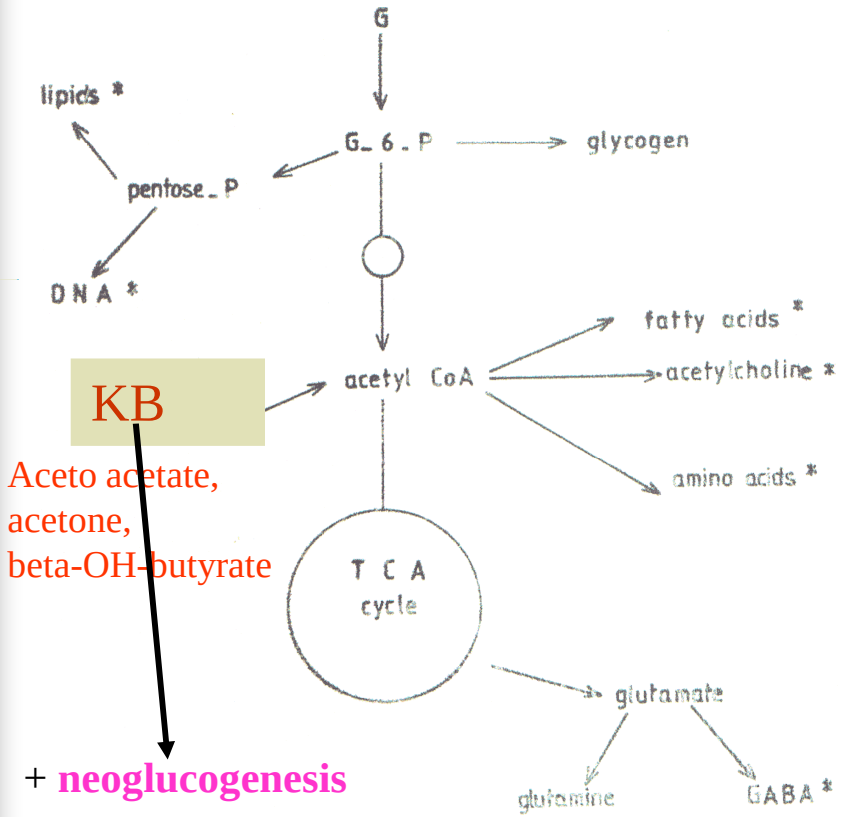
- Decreasing availability of glucose AND increasing availability og KB
- Increases the contents of ATP in brain
- increases the contents of GABA in some areas
- more stability of Na+, K+ an Ca+ channels
- increases thresholds of epileptogenesis

Contra-indications of ketogenic diet

- Pyruvate carboxylase deficiency
- organic aciduria, defect of ketogenesis
- mitochondrial diseases (+/-)
- porphyria
- defects in FA oxydation
- carnitine deficiency
- glutaric aciduria type II
- pyruvate dehydrogenase phosphate deficiency
- Long QT

--> Central role of **glucose** for energy an synthesis

--> **Ketone bodies** go inside mitochondria for ATP production; also FR scavenger, antiangiogenic effect, and stimulates glutathione peroxidase activity



- ATP and 5-Pentose;
- In- and out-cells composition
- neurotransmission
- Defenses against FR and EAA
- BMR
- Muscles (FFA) and intestines (glutamine and KB) have alternatives

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Typical methodology for ketogenic diet

- Prehospital evaluation of infants ' health and family motivation
- preparing medical and nursing team for the individual case admission
- hospitalization for a 4 weeks trial
- implementing the follow-up phase

The typical course of the hospital phase

- Calculating the regime *:

1.ratio L/P = 4/1 (calories: 90 % Lp, 12 % Pt, 2 % CH), in 4 to 6 meals.
Ketogenesis is fully obtained afer 2-5 days (acetest in urines +++).

2. Caloric intakes: 1200 --> 1500 kcal/sqM;

3. Supplement in NaCl, KCl, Ca++, P and Mg

4. Fluids intakes: 2000 ml/sqM

5. Cautions to avoid any intake from sugars (see drugs and nutrition)

- using Ketocal:

20g/100 ml -->

21 mosmol, 14.6 g Lp, 3.1 g Pt, 0.6 g CH, 146 kcal , 4.3 mmol Na+, 4.1 K+, 86 mg Ca++, 86 mg P, 22 mg Mg + vitamins (ie Omnibionta.

- Free ketogenic diet software:

http://www.stanford.edu/group/ketodiet/

DIET: PRACTICAL ASPECTS

- Fasting period: no long needed
- Restriction of fluids intake can be harmful
- Start with 75 to 100% of energetics requirements
- Ketocal is useful but not obligatory
- Ketogenic diet 4/1 without fasting period can achieve satisfying ketosis in 24 to 48 hours
- Before 3 years, start with KD 3/1
- Practically, ketogenic diet is computed using (1) energetic needs, (2) minimal proteic needs and (3) ketogenic ratio

DIET: PRACTICAL ASPECTS

Age	**Daily Energetic needs** kcal/kg of "ideal weight"	**Daily Minimum protein Requirement** g/kg of ideal weight
0 - 18 months	**110 - 90**	**2.2 à 1.8**
18 months – 3 years	**90**	**1.8 à 2**
1-4 years	**90**	**1.6 à 2**
4-7 years	80	1.1
7-10 years	72	1.0
10-13 years	60	1.0
13-15 years	52	1.0
Male (adult)	30 - 35	1 (max 50g)
Female (adult)	25 - 30	1 (max 50g)

DIET: PRACTICAL ASPECTS

- Diet Unity:

« Ketogentic diet unity » is derived from the ratio between fat and non-fat in the diet

Ketogenic diet	Fat		non-Fat		Diet Unity
1 to 1	1 x 9 kcal	+	1 x 4 kcal	=	13 kcal
2 to 1	2 x 9 kcal	+	1 x 4 kcal	=	22 kcal
3 to 1	3 x 9 kcal	+	1 x 4 kcal	=	31 kcal
4 to 1	4 x 9 kcal	+	1 x 4 kcal	=	40 kcal
5 to 1	5 x 9 kcal	+	1 x 4 kcal	=	49 kcal

DIET: PRACTICAL ASPECTS

- Example: KD 4/1 : Diet Unity = 40

A… kcal : 40 = …. X 4 =	... g of fat X 9 =	…. kcal
A… kcal : 40 = …. X 1 =	… g of non fat	
Minimum protein requiremen =	B… g of protein X 4 =	…. kcal
	C.. g glucides X 4 =	…. kcal
	TOTAL	F… kcal

DIET: PRACTICAL ASPECTS

- Example: KD 4/1 : Diet Unity = 40

1000 kcal : 40 = **.25** X 4 =	**100**... g of fat X 9 =	**900**. kcal
1000… kcal : 40 = **25** X 1 =	**25**… g of non fat	
Minimum protein requiremen =	**20** g of protein X 4 =	**80**. kcal
	5.. g glucides X 4 =	**20** kcal
	TOTAL	**1000** kcal

Monitoring and guidelines for hypoglycemia

- Monitorring during hospital phase
  - Glycemia, cetonuria, heart rate, respiratory rate, BP
  - 8, 11, 17, 20, 24h
  - Daily weight
  - Look for: agitation, weakness, tachycardia, sweating, pallor, faintness, alteration of consciousness

Monitorring and guidelines for hypoglycemia

If blood glucose < 0.4 g/l				
Without clinical signs of hypoglycemia		**With clinical signs of hypoglycemia**		**In infants younger than 18 months**
BETWEEN 0.30 AND 0.40 g/l Check and reapeat glycemia after 2 hours.	**< 0.25 g/l** Intensify monitoring	**WITHOUT ALTERATION OF CONSCIOUSNESS** Give 50 ml of orange juice and close monitoring of the patient, check glycemia hourly	**WITH ALTERATION OF CONSCIOUSNESS OR GLYCEMIA < 0.25 g/l** Blood sampling and Perfusion with glucose 10%, bolus of 4 ml/kg. followed by continuous perfusion at 4 ml/kg/h et **stop ketogenic diet**	**GLYCEMIA < 0.25g/l (WITH OR WITHOUT)** Blood sampling Perfusion with glucose 10%, bolus 4ml/kg followed by 4 ml/kg/h and **stop ketogenic diet**

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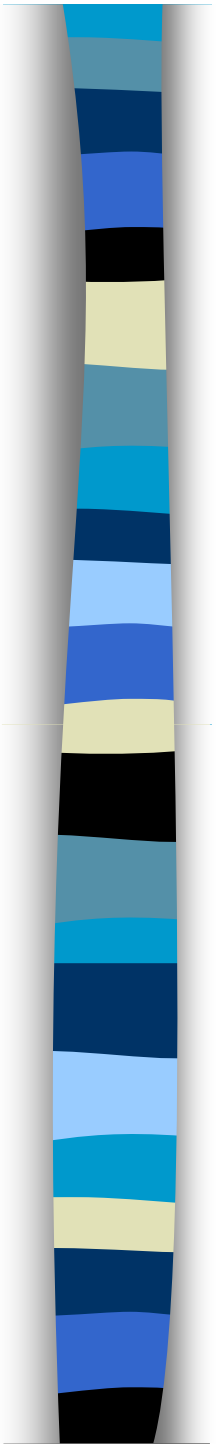
The follow-up phase

- Ketonuria: twice a week
- ++ to +++
- If ++++
  - Dehydratation?
  - Deficient caloric intakes?
  - Excessive diet? (4/1 → 3/1)

The follow-up phase: from time 0 = end of hospitilization

- After 2 weeks: clinical examination
- after 6 weeks: clinical + ECG + EEG + biology (blood and urines)
- after 14 weeks : clinical + EEG + biology
- after 18 weeks: clinical + biology
- after 26 weeks: clinical +EEG + biology
- after 36 weeks: clinical + biology + EEG + abdominal US
- after 44 weeks: clinical + biology
- afterwards till the end: every trimester, clinical and evry semester add EEG, ECG and abdominal US



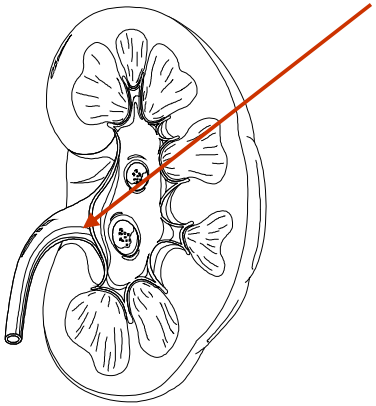
Surveillance of ketogenic diet: clinics, biology, electrophysiology, imaging

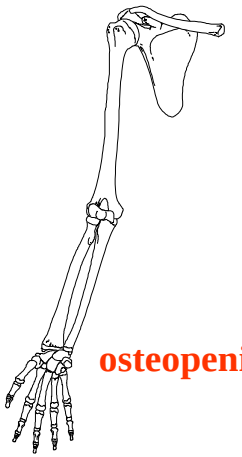
- **Clinics:** neuro-developpemental and also owing to difficulties such as psychology, GER, constipation, hemodynamics

- **Biology** (blood and urines): neurology and metabolism oriented, and also think on liver, kidneys, electrolytes
- **electrophysiolgy:** EEG, ECG
- **imaging:** neurology oirented and also think on biliary and urinary systems.

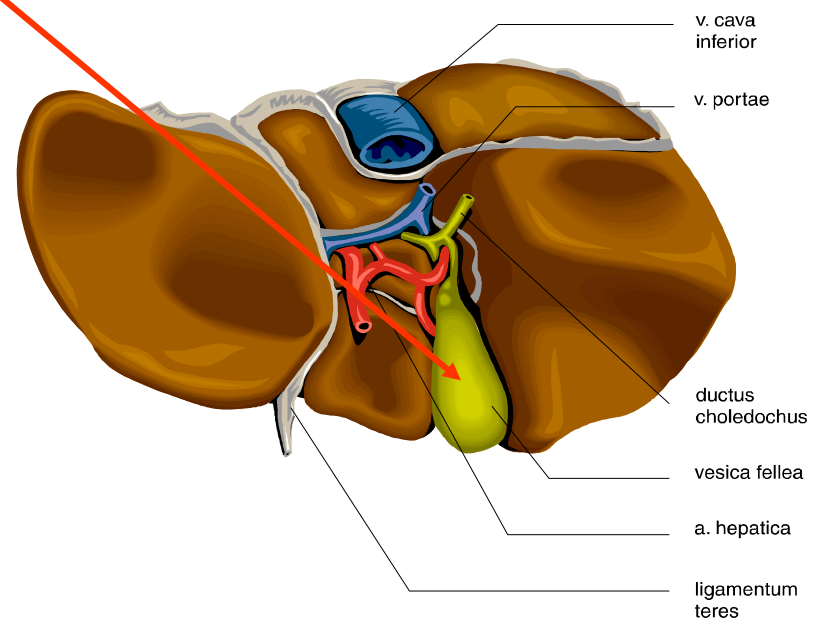
Think on extracerebral difficulties or complications

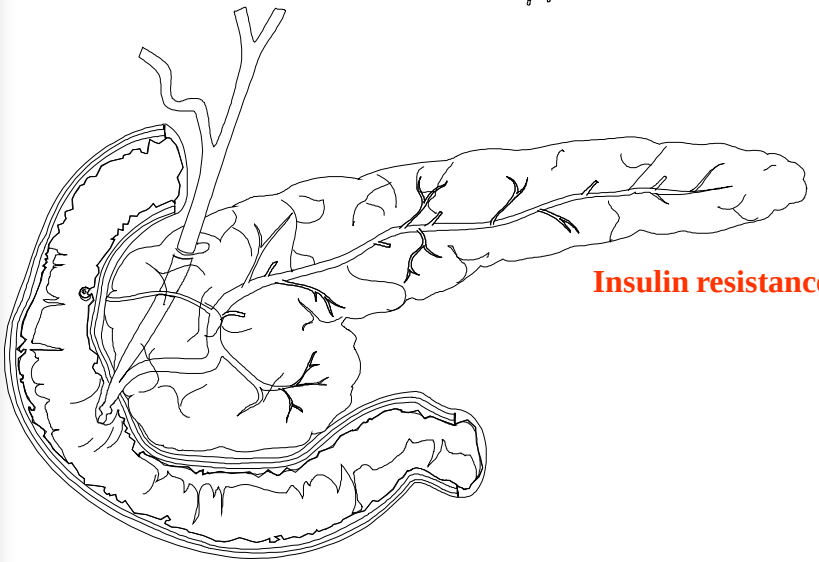
stones





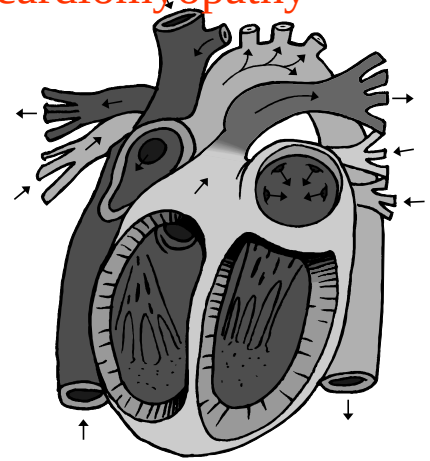
osteopenia





Insulin resistance

cardiomyopathy



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Brain oncology and ketogenic diet
(Zhou and coll ; Seyfield , Boston college, 2007

- Astrocytoma (in mouse) and glioma (in human)

-- > anti-tumor properties

--> anti-inflammatory properties

--> anti-angiogenic properties

--> pro-apoptotic properties

- tumors are unable to consume ketone bodies.

Ketogenic efficiency in epilepsy: panorama of results from John Hopkins (Groesbeck et al, Freeman).

- Efficiency : in 30-35 % of cases

=

--> free of seizure	7%
--> free of medication	36 %
-->control with 1 medication	34 %
--> reduction of seizure in frequency	27 %

- middle efficiency: in 30-40 % of cases

= reduction of frequency of seizures by more than 50 %

- no efficiency and discontinued = 25-30 % of cases

too restrictive, intermittent ilnesses.

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