Question 1: Inborn errors of creatin metabolism & transport
(13 points)

The cerebral creatine deficiency syndromes, inborn errors of creatine metabolism, include the two creatine biosynthesis disorders and the creatine transporter deficiency.

A) Which two enzymes are needed to synthesize creatine in the body? (2 points)

2 enzymes: The names are AGAT and GAMT

B) Is it possible to restore the creatine levels in the brain of a patient with a creatine transporter defect? Motivate your answer and include in your answer: type of treatment, experience in patients, rational based on the metabolic pathway. (4 points)

At the moment this is not possible. The creatine transporter is needed to transport creatine into brain cell. In patients with creatine transporter defect this transporter is not functioning due to an inherited mutation in this gene, and thus creatine is expected not to be restored in the brain of patients with this defect. This is indeed what was reported in patients who were treated with creatine.

C) Is it possible to restore the creatine levels in the brain of patients with a creatine biosynthesis defect? Motivate your answer and include in your answer: type of treatment, experience in patients, rational based on the metabolic pathway. (4 points)

Yes this is possible. The creatine transporter is needed to take up creatine in the brain cells. It has been shown by brain MRS that the creatine pool can almost be restored in both biosynthesis disorders. In AGAT defect creatine supplementation is given. In GAMT, in addition to creatine ornithine is given.

D) Which of these 3 types of creatine disorders is the best candidate to be included in the newborn heelprick screening? Please explain in not more than 5 lines why you came to this conclusion and include all tree disorders in your answer. (3points)

GAMT deficiency, since this is a disorder when treated early in life disease progression can be stopped and there is a metabolite marker (guanidionacetate) that can be measured in blood spots. For AGAT deficiency, treatment is also available but so far no pathognomic marker is detected in blood spots. CTD: no marker available in blood spots and no treatment so far

Question 2: What a doctor should know about clinical chemistry (7x 1 point)

What are important pre-analytic issues one needs to take into account when drawing blood for clinical analysis? Name 7.

1. Time of blood taking (important for analytes with a day-night rhythm)
2. Fasting or not
3. Is a special diet needed?
4. Type of tube used for drawing blood (do you need serum, EDTA plasma or heparine plasma?)
5. Performing the prodcedure correctly (removing the tourniquet in time, inverting the tube)
6. Indentification of the patient and checking whether the identification on the tube
7. Checking whether the patient uses any medications that could affect in vivo or in vitro the analysis (eg. Heparine affects the free T4 determination)

Question 3: Development of the mammalian immune system
(6 points/phase, total of 12 points)

Lymph node development occurs in several phases.
Describe the first two phases of lymph node development. Include the different cells, chemokines and molecules that are involved in these processes.

1) Initiation= RA secretion by neurons, induction of CXCL13 by adjacent mesenchymal cells, attraction of first (precursor) LTi cells, interaction between these first LTi cells to upregulate LTalphabèta on their surface.

2) Definitive formation=LTalphabèta – LTbètaR signaling through the interaction of LTi cells and stromal organizers, respectively. This leads to the expression of chemokines, adhesion molecules and cytokines, by which additional cells are attracted, retained, and stimulated to survive.

Question 4: Effects of human milk on the immune system
(2x 5 points)

Beneficial effects of breastfeeding are well-recognized and include both immediate neonatal protection against pathogens and long-term protection against allergies and autoimmune diseases. Fucosylated glycans in human milk, such as those expressed in oligosaccharides or on glycoproteins, play an important role in protecting the infant against infectious agents. Nevertheless, the degree of protection from infectious disease in breastfed infants significantly varies between mothers. (2x 5 points)

A) Why does this level of protection vary between mothers (and their milk)?

A) It depends on the secretor status of the mother and thus the type of fucosylated glycans present

B) Why is human milk far superior in its protection against infection compared to cow's milk or formula milk?

B) Cow's milk and formula milk have a completely different glycan profile and thus not target the right receptor (DC-SIGN).

Question 5: Feeding and IGF-1
(3x 4 points)

Poor postnatal growth after preterm birth does not match with the normal rapid growth in utero and is associated with preterm morbidities. Insulin-like growth factor 1 (IGF-1) axis is the major hormonal mediator of growth in utero. IGF-1 action mainly occurs during the period of rapid rise in utero i.e. during the postmenstrual age of 22-40 weeks. After preterm birth levels of IGF-1 fall and remain often very low for weeks to months. This may result in a delay of growth and development during this extra uterine period corresponding in time with the third trimester of pregnancy. There have been many reports of correlations between low IGF-1 in preterm infants in the first weeks to months and complications of prematurity leading to serious morbidities.

Describe 3 morbidities of prematurity resembling developmental abnormalities in growth. (3x 4 points)

There have been many reports of correlations between low IGF-1 and complications of prematurity. These complications resembled many developmental abnormalities of growth and included:

1. abnormalities of general growth and body composition –leading to obesity-
2. lung immaturity -leading to bronchopulmonary dysplasia- ,
3. poor postnatal vascular development in the setting of early retinopathy – leading to ROP and long term risk of cardiovascular disease–
4. brain developmental abnormalities-leading to deficits in cognitive function-
5. metabolic derangement, such as insulin insensitivity.

Question 6: **Adrenocortical function in early life**
(10 points)

A 9-day old male newborn has a positive heelprick screening for adrogenital syndrome. You are informed about this and decide to see the child the same day at the outpatient department for pediatrics.

A) What are the most important parameters you look at during the physical examination? Name 2 parameters. (2x 2 points)

A) consciousness, Weight, Hydration, Heart rythm

B) Which are, according to the guidelines, the designated laboratory tests to order first? Name 3 (3x 2 points)

B) Sodium (Natrium), Potassium (Kalium), Glucose, 17-OH progesteron

Question 7 was removed from the final exam.

Question 8: **Prematurity: cardiometabolic risk factors as child and adult**
(4 points)

In children born after the hunger winter various long-term health effects have been described. As adults, some have mainly dyslipidemia and increased cardiovascular disease risk, whereas others have mainly glucose intolerance and type 2 diabetes.

Which factor explains the difference between the two groups?

The trimester during which the mother experienced the most severe hunger period.

Question 9: The severely ill child
(5 points)

The respiratory quotient is calculated as the ratio of VCO2/VO2. Its value normally is found between 0.7 and 1.0. RQ is influenced by substrate use, eg carbohydrates and fats, but also by over- or underfeeding.

Would you expect RQ to be lowered or increased by underfeeding, e.g. there is insufficient substrate to be oxidized)? Explain your answer.

Underfeeding will decrease/lower RQ. During underfeeding the body switches to burning fat instead of glucose. Glucose has an RQ of 1 and fat an RQ of 0.7. Thus, the RQ will decrease.