CANADIAN COLLEGE OF MEDICAL GENETICISTS (CCMG)
Biochemical Genetics Specialty Examination

May 4, 2010

Duration: 3 hours

Total Pages: 12 (including cover page)

Total Marks: 105

Instructions:

1. Please ensure that your candidate number is on each page of your answer booklet. Do not use your name.

2. Please write in dark blue or black ink. Do not use pencil.

3. Each question may be answered in point form with tables and diagrams where appropriate. Please show all calculations.

4. Please return all exam materials at the end of the examination.
Section A: Short answer questions. Please answer 6 of 8 questions only. Do not answer more than 6 questions as only 6 answers will be graded. Each has a value of 10 marks.

If you choose to answer question 3, please indicate in your exam booklet on top of a new page “I circled my answers to question 3 directly on the exam”. If you choose to answer question 5, please indicate in your exam booklet on top of a new page “I answered question 5 directly in the table” and proceed to fill the table.

Question 1.

Describe five (5) criteria that should be met for a disorder to be considered appropriate for a newborn screening program. Choose one (1) metabolic disorder as an example and describe how newborn screening for this disorder meets each of the five (5) criteria (2 marks per criteria).

Question 2.

You are asked to complete the diagnostic evaluation of a newborn baby found to have a high forehead with wide fontanelles, seizures, hypotonia, hyperbilirubinemia, and stippling of several long-bones on a skeletal survey.

1. What is the most likely diagnosis? 1 mark
2. List five (5) laboratory tests that you would expect to be abnormal in this disorder. Explain the rationale for the selection of tests and the expected results. 9 marks
Question 3. Answer all four multiple choice questions (MCQ), by circling the correct numbered answer. Each MCQ is 2.5 marks.

MCQ1) The CDGs have been classified as type I or type II. What is the difference?
   A) The isoelectric focusing pattern of transferrin isoforms may distinguish one type from the other.
   B) CNS involvement is prominent in one type, but not in the other.
   C) In one type, the enzyme abnormalities are cytosolic, while in the other the defects are intraluminal in the endoplasmic reticulum (ER)
   D) Whereas one type responds well to treatment, the other is resistant to specific therapy.

Circle the correct numbered answer:
   1) A, B and C are all correct
   2) Only D is correct
   3) A and C are correct
   4) None is correct
   5) All are correct

MCQ 2) Isoelectric focussing of transferrin may produce false positive test results in which of the following situations?
   A) Chronic alcoholism
   B) Galactosemia
   C) Hereditary fructose intolerance
   D) Glycogen storage disease type 1b

Circle the correct numbered answer:
   1) A, B and C are all correct
   2) Only D is correct
   3) A and C are correct
   4) None is correct
   5) All are correct
MCQ 3) Which of the following are clinical features common to almost all patients with CDG type I?
   A) Psychomotor retardation
   B) Seizures
   C) Failure to thrive
   D) Diarrhea

Circle the correct numbered answer:
   1) A, B and C are all correct
   2) Only D is correct
   3) A and C are correct
   4) None is correct
   5) All are correct

MCQ 4) CDG syndrome may present with:
   A) Seizures
   B) Cerebellar hypoplasia
   C) Inverted nipples
   D) Neonatal hypoglycemia

Circle the correct numbered answer:
   1) A, B and C are all correct
   2) Only D is correct
   3) A and C are correct
   4) None is correct
   5) All are correct
Question 4.

Your laboratory has been analyzing amino acids with a dedicated amino acid analyzer (using an ion-exchange column and ninhydrin). To your satisfaction, your request for capital equipment has been approved. Your laboratory will purchase a tandem mass spectrometer dedicated for the analysis of amino acids.

1. List one (1) advantage and one (1) disadvantage of tandem mass spectrometry compared to your previous method. 2 marks
2. List three (3) laboratory procedures involved in validating this new test. 3 marks
3. List and briefly explain two (2) methods of monitoring your assay performance. 2 marks
4. List three (3) administrative steps involved in introducing this new test / instrument. 3 marks
Question 5.

Each row of the table below refers to a single enzyme, deficient activity of which leads to a characteristic pattern of metabolite abnormalities and to clinical disease. In each case, the biochemical and clinical abnormalities MAY normalise or improve in response to a particular vitamin or cofactor. Complete the table.

<table>
<thead>
<tr>
<th>Deficient enzyme</th>
<th>Name any ONE metabolite typically at abnormal levels in PLASMA</th>
<th>Name any ONE metabolite typically at abnormal levels in URINE</th>
<th>Potentially responsive to which vitamin or cofactor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine hydroxylase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Branched-chain α-keto acid dehydrogenase complex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystathionine β-synthase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfite oxidase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-aminoadipic semialdehyde dehydrogenase</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Question 6.

A number of treatments have been proposed for Niemann-Pick disease.

1. Enzyme replacement therapy is under development for Niemann-Pick disease Type B. Describe the main principles and limitations of enzyme replacement therapy for lysosomal storage disorders and why NP-B, but not NP-A, is being targeted for therapy. 6 marks

2. Miglustat (Zavesca) has been evaluated in clinical trials for the treatment of Niemann-Pick disease Type C. Describe a possible mechanism of action of this drug in the treatment of NP-C. 4 marks

Question 7.

A female patient with PKU (Susan Smith) considers that she is ready for pregnancy and she comes to clinic for consultation. You request an amino acid profile prior to your consultation with this patient. The phenylalanine level is 1200 µmol/L and the tyrosine level is 86 µmol/L.

1) Explain and describe the potential effect of high maternal PHE on the fetus. 3 marks
2) What clinical features might you see in poorly controlled maternal PKU at birth? 2 marks
3) What three (3) recommendations would you give for treatment for this patient? Include target PHE range in your answer. 3 marks
4) If Susan first came to your clinic at 4 weeks gestation with a PHE of 1200 µmol/L, what would the prognosis be? Explain. 2 marks

Question 8.

A pregnant patient had prenatal screening for Down syndrome. Your laboratory performed second trimester screening test. Your laboratory technologist is showing you the screening report.
The patient is 31 years old. The gestational age is 15 weeks 4 days. The report indicates that the patient is screen negative for Down syndrome. The only abnormal result from the second trimester screening is an extremely low estriol. The laboratory value is 0.5 nmol/L, with a corresponding 0.16 MoM (multiple of medians) for uE3.

a) What is the differential diagnosis for this finding? 3 marks
b) State two (2) laboratory investigations you would recommend to establish a diagnosis. 4 marks
c) List three clinical features associated with one (1) diagnosis named in your answer (a) above. 3 marks
Section B: Long answer questions. Please answer 3 of 5 questions only. Only 3 answers will be graded. Each has a value of 15 marks.

Question 1.

A 5-month-old male infant presents with hypertrophic cardiomyopathy, marked hypotonia and muscle weakness, enlarged tongue and mild hepatomegaly. There is no evidence of involvement of any other organs, and mental development appears normal.

a) State the most likely diagnosis, and identify the relevant enzyme and a brief description of its normal physiological role. 3 marks
b) Suggest one (1) “routine chemistry” parameter which might be abnormal in this disorder. Provide a short explanation why it would be abnormal. 1 mark
c) Discuss the range of clinical phenotypes of this disorder if untreated. 3 marks
d) You wish to confirm your working diagnosis by enzyme assay. Identify practical advantages and disadvantages of three (3) sample types, and where appropriate strategies to optimise assay specificity. 3 marks
e) The patient is found to be “CRIM-negative” for this enzyme. Explain what this means, and the likely implications for prognosis and response to therapy. 3 marks
f) DNA testing shows the infant to have two known pathogenic mutations, one present in mother’s DNA, the other present in father’s DNA. However, the mother is also found to carry a novel missense mutation not found in the infant. What are the implications of this result for the mother? Suggest two (2) possible interpretations (other than laboratory error). 2 marks
Question 2.

A female infant presents in the first few days of life with progressive lethargy, hypotonia, myoclonic jerks and apneic episodes. Routine chemistry investigations show mild respiratory acidosis but no other abnormalities. Analysis of plasma amino acids shows glycine of 1200 μmol/L (reference interval 110 – 280), with unremarkable values for all other amino acids.

a) What is the most likely diagnosis? 1 mark
b) What other disorders are in your differential diagnosis? 1 mark
c) Urine and CSF were collected at the same time as the plasma. What tests would you order and how would the results help to support your working diagnosis and to rule out other possibilities? 2 marks
d) Explain how CSF sample quality can affect results and interpretation. 2 marks
e) Why is it important to clearly establish the diagnosis as soon as possible? 2 marks
f) Explain two (2) ways the diagnosis of this disorder could be confirmed. Discuss the one (1) advantage and one (1) disadvantage of the two (2) approaches. Include a brief description of the enzyme and the gene(s) in your answer. 5 marks
g) Suggest two (2) reasons why population newborn screening for this disorder is not widely performed. 2 marks
Question 3.

A 24-year-old woman presents with a history of progressive muscle weakness.
Based on the pedigree shown below and the table with the clinical information below, you have a strong suspicion of the underlying etiology;
1) What is the most likely pattern of inheritance? 2 marks
2) Which individuals in the pedigree help to discern the etiology? Explain. 5 marks
3) Discuss disease pathophysiology at the DNA, tissue/organ, and clinical phenotype level. Illustrate each point by specific reference to this pedigree / clinical scenario. 8 marks

Pedigree to long question #3.

Refer to table for clinical information.
<table>
<thead>
<tr>
<th>Individual</th>
<th>Condition</th>
<th>Individual</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>Deceased, colon cancer, 55years</td>
<td>II-7</td>
<td>Rheumatoid arthritis, 41years</td>
</tr>
<tr>
<td>I-2</td>
<td>Arthritis, 78years</td>
<td>III-1</td>
<td>Healthy, 30years</td>
</tr>
<tr>
<td>I-3</td>
<td>Healthy, 79years</td>
<td>III-2</td>
<td>Progressive visual impairment, 28years</td>
</tr>
<tr>
<td>I-4</td>
<td>Coronary artery disease, 77years</td>
<td>III-3</td>
<td>Developmental delay NYD, 6years</td>
</tr>
<tr>
<td>II-1</td>
<td>Healthy, 50years</td>
<td>III-4</td>
<td><strong>Proband</strong>, 24years</td>
</tr>
<tr>
<td>II-2</td>
<td>Healthy, 45years</td>
<td>III-5</td>
<td>Hypertrophic cardiomyopathy, 19years</td>
</tr>
<tr>
<td>II-3</td>
<td>Diabetes on insulin, 44years</td>
<td>III-6</td>
<td>Deceased, pneumonia, 6years</td>
</tr>
<tr>
<td>II-4</td>
<td>Peripheral neuropathy, 46years</td>
<td>III-7</td>
<td>Deceased, “acidosis”, 6months</td>
</tr>
<tr>
<td>II-5</td>
<td>Healthy, 45years</td>
<td>III-8</td>
<td>Healthy, 18years</td>
</tr>
<tr>
<td>II-6</td>
<td>Progressive ataxia, 43years</td>
<td>III-9</td>
<td>Retinitis pigmentosa, 16years</td>
</tr>
</tbody>
</table>
Question 4.

You receive a “low free carnitine” screening result from the provincial newborn screening program on a 9-day-old male from a sample obtained at 48 hours of age. You call the family doctor to discuss this result and find that she is seeing the baby and his mother in 30 minutes for a routine post-natal visit.

1. Give three (3) mechanisms that could have led to the low free carnitine levels at 48 hours of age in this baby. 3 marks
2. List and explain three (3) clinical signs that the family doctor can detect on physical exam to help narrow your differential diagnosis. 6 marks
3. List and explain three (3) laboratory tests that should be done now to narrow down your differential diagnosis. 6 marks

Question 5.

3-methylglutaconic acid levels can be elevated in the urine for a variety of reasons.

1. List three (3) types of 3-methylglutaconic acidurias and discuss how the organic acid pattern in the urine can help differentiate between them. 3 marks
2. Discuss four (4) other key clinical or laboratory features that can further delineate EACH of the three types of 3-methylglutaconic acidurias you listed above. 12 marks