Duration: 3 hours

Total Marks: 105

Total Pages: 8

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 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. Only the first 6 answers will be graded. Each has a value of 10 marks. If you choose to answer questions 1 and/or 7, please indicate in your exam booklet on top of a new page “I answered question 1 (or question 7) directly in the table” and proceed to fill in the table.

Question 1.

The following table includes three disorders that cause hyperphenylalaninemia (HPA) in infants and children. Please complete the table.

<table>
<thead>
<tr>
<th>Please complete the following:</th>
<th>Causes for HPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dihydropteridine reductase deficiency</td>
</tr>
<tr>
<td>Urinary levels of neopterin (answer as: decreased, within reference intervals, increased) (use as many as required)</td>
<td></td>
</tr>
<tr>
<td>Urinary levels of biopterin (answer as: decreased, within reference intervals, increased)(use as many as required)</td>
<td></td>
</tr>
<tr>
<td>Urinary neopterin/ biopterin ratio (answer as: decreased, within reference intervals, increased)(use as many as required)</td>
<td></td>
</tr>
<tr>
<td>Urinary % BH₄, i.e. BH₄ as percentage of total biopterin (answer as: decreased, within reference intervals, increased) (use as many as required)</td>
<td></td>
</tr>
<tr>
<td>Which sample type and test would you recommend for confirmation of diagnosis?</td>
<td></td>
</tr>
<tr>
<td>Outline of treatment at time of diagnosis (drug dosage not required)</td>
<td></td>
</tr>
</tbody>
</table>
Question 2.
You receive a urine specimen from a one-month-old male, with a request for organic acids analysis. The sample was sent in from a remote location, without any clinical information, and you have not yet been able to contact the requesting physician. The organic acids profile is dominated by greatly elevated 4- hydroxyphenylpyruvate, 4-hydroxyphenyllactate and 4-hydroxyphenylacetate.

   a) Name two (2) metabolic disorders in the differential diagnosis. For each condition, identify the deficient enzyme and two typical clinical features. Briefly discuss the treatment options for one of these disorders.
   
   b) Describe two (2) common reasons for such a profile, other than metabolic disorders.
   
   c) What further studies on the urine sample could help you narrow the differential? Summarize your approach, including its limitations.

Question 3.
A 6-day-old Chinese male infant presenting with conjugated hyperbilirubinemia has a positive Beutler galactosemia screening test (a semi-quantitative fluorometric test done on dried blood spots based on the fluorescence generated by the reduction of NADP⁺ to NADPH). His mother is known to be a carrier of glucose-6-phosphate dehydrogenase (G6PD) deficiency. How does this influence your interpretation of the screening test results? What further investigations would you recommend to confirm a diagnosis?

Question 4.
Your laboratory is the regional referral center for the measurement of acylcarnitines (species identification and quantitation). The tandem mass spectrometer that is dedicated for this specialized testing is due for a major preventive maintenance. The vendor indicated that the technical specialist will be on-site and the instrument will not be available for three consecutive days. Please describe at least four (4) actions that you will take before proceeding to instrument downtime.

Question 5.
You are overseeing the follow-up of “screen positive” results for your province’s newborn screening program. A bloodspot from a 3-day-old male shows clearly elevated C5OH-acylcarnitine, and a repeat bloodspot collected at 8 days of life confirms that finding.

   a) List six (6) inherited metabolic disorders in the differential diagnosis.
   
   b) Give two (2) examples of situations where increased C5OH carnitine can be seen in an infant or child who does not have any primary metabolic disorder.
   
   c) Choose any TWO of the disorders from a). Use one disorder to make a point FOR inclusion of C5OH-acylcarnitine in a newborn screening program and another disorder to make a point AGAINST.
d) Summarize the differences and similarities between the urine organic acid profiles seen in the two disorders selected in c).

**Question 6.**
A clinical geneticist in your Hospital has recently seen a child suspected of having Hartnup disease. Provide two (2) clinical features that are associated with this disease. Indicate how this clinical diagnosis can be confirmed in your biochemical genetics laboratory. Your colleague clinical geneticist is asking you the recommended treatment for this disorder.

**Question 7.**
The table summarizes results from hexosaminidase assays performed on serum, using an artificial substrate with heat inactivation to discriminate between the isoenzymes. Samples from patients 1, 2 and 3 were submitted for testing of infants with developmental regression. Samples from patients 4, 5, 6, 7 and 8 were submitted for “carrier testing” on adults of Ashkenazi-Jewish origin.

<table>
<thead>
<tr>
<th>Reference interval</th>
<th>Total hexosaminidase activity (nmol/hr/mL)</th>
<th>Hexosaminidase A activity (nmol/hr/mL)</th>
<th>Hexosaminidase A as a percentage of total hexosaminidase activity</th>
<th>Most likely diagnosis (please complete)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>710 – 1,920</td>
<td>530 – 1,080</td>
<td>58% - 78%</td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>473</td>
<td>27</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>40</td>
<td>25</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>17,700</td>
<td>10,266</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>787</td>
<td>535</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>458</td>
<td>376</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Patient 6</td>
<td>2,152</td>
<td>839</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Patient 7</td>
<td>683</td>
<td>321</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Patient 8</td>
<td>881</td>
<td>520</td>
<td>58%</td>
<td>1)</td>
</tr>
</tbody>
</table>

a) For patients 1 to 7 (inclusively), please complete the table indicating the single most likely explanation for their results.

b) For patient 8, provide three (3) possible explanations for the results, and describe how you would distinguish between these possibilities.

c) Patients 5 and 7 are partners. After further testing has confirmed your original interpretations of their serum results, they seek pre-conception counselling. Explain what advice you could provide.
Question 8.
You have been consulted on a three-year old child with severe mental retardation and low urine and plasma creatinine levels. The laboratory received 10mL of plasma sample and 25mL of random urine sample.

a) Provide the metabolic pathway that is important to explain the decreased creatinine levels
b) Outline the differential diagnosis
c) Briefly describe the laboratory tests you would request (including enzyme testing)?
d) Discuss the possible laboratory findings with all the diseases included in your differential diagnosis

Section B: Long answer questions. Please answer 3 of 5. Only the first 3 answers will be graded. Each has a value of 15 marks.

Question 1.
A 7-year-old Greek immigrant boy presents with a history of deteriorating attention span, distractibility, and social withdrawal. An MRI of the brain shows increased signal in a posterior periventricular distribution on T2-weighted images. He is the youngest of three boys born to young, healthy, unrelated parents. He had a cousin, the son of his mother’s sister, who died 3 years ago of some neurodegenerative disease at age 10 years.

a) Discuss a differential diagnosis, including appropriate laboratory investigation, and indicate the most likely diagnosis.

b) List the phenotypic variability of your most likely diagnosis, including the relative frequency of the different variants.

c) List three (3) points that you consider particularly important to cover in genetic counselling of the parents and other members of the family.

d) Summarize the key recommendations you would make with respect to treatment of the proband and other at-risk members of the family.
**Question 2.**
You have been asked to advise on a 9-month-old child born in Africa who presented with 2 days of vomiting and poor intake, and was poorly responsive and had a seizure in the ER. The initial glucose level when in ER was reported as <1mmol/L. IV glucose has been given and the child is waking up. Subsequent blood sugar measurement was 3.0mmol/L, the lactate, ammonia and venous gas were normal. The physical examination is normal other than lethargy. Birth history is normal; development is appropriate for age. There has been no recent change in diet. A first cousin died in Africa with “SIDS” at age 4-months.

a) List four (4) groups of disorders in your differential diagnosis. For each group, outline one reason favouring and one reason against the likelihood of this diagnosis.

b) What laboratory tests would you request, including routine and biochemical genetics tests?

The results of these laboratory tests suggest a defect of fatty acid oxidation:

c) Outline the metabolic pathway deficient in fatty acid oxidation defects (chemical structures not needed). You can draw and/or write in text.

d) What is the most common fatty acid oxidation defect?

e) Describe three (3) laboratory tests that you would request to confirm the diagnosis, with the expected results.

f) Outline two (2) recommendations for treatment for the most common fatty acid oxidation defect.

**Question 3.**
A 32-year-old Ashkenazi-Jewish woman experiences a significant postpartum hemorrhage as a result of thrombocytopenia associated with enlargement of the spleen and liver. Investigation shows she has marked deficiency of beta-glucosidase in peripheral blood leukocytes consistent with a diagnosis of Gaucher disease.

a) Discuss what further investigations you would undertake to assess her risk for having subacute neuronopathic (type 3) Gaucher disease.

b) Summarize genotype-phenotype correlations in Gaucher disease (all types of Gaucher disease).

c) List six (6) complications experienced by patients with Gaucher disease (all types of Gaucher disease) and how each selected complication might be expected to respond to enzyme replacement therapy (ERT) with imiglucerase (Cerezyme®).

d) Discuss two (2) advantages and two (2) disadvantages of premarital screening for carriers of Gaucher disease.
**Question 4.**

You have been asked to meet with a 22-year old man, Robert, in your Genetics clinic. Yesterday (Sunday), Robert went for a long run. He estimated that he ran a half-marathon (approx. 21 km). Sunday night, he had burgundy urine. He went to the emergency department where he met with the attending emergency physician. Robert indicated that his paternal grand-father, George, was diagnosed by a neurologist with glycogen storage disease type V when George was a young adult.

Specimen collection was performed: blood and urine samples were collected, sent to the laboratory and stored at 4°C; and a consultation with Genetics was organized for Monday AM.

a) What is the biochemical defect in glycogen storage disease type V?

b) Explain what is the main enzymatic role of the enzyme responsible for glycogen storage disease type V and what are the biochemical consequences of its deficiency. (You can answer with diagram and/or text).

c) Explain the reason for the burgundy color of the urine.

d) You have access to biological samples (urine, EDTA whole blood, serum and plasma) that were collected at time of presentation in the emergency department. What first-line laboratory tests might help you to confirm or rule out the diagnosis of glycogen storage disease type V? Name them and present the rationale for requesting them and the expected results.

e) How could you establish a definitive diagnosis in your patient?

f) What are the treatment options for Robert? Provide three (3) options.

g) The family history cannot be confirmed yet, since you do not have access to diagnostic laboratory reports from George’s file. George lives 500 km away from your clinic and the investigations were not conducted at your center. Are there other inborn errors of metabolism that could explain Robert’s clinical presentation?

**Question 5.**

A 6 month old infant presents with acute lactic acidosis and seizures. Past history is normal except for mild developmental delay. There is no sign of infection and physical examination is normal aside from mild hypotonia. This is the couple’s first child, and family history is noncontributory. Laboratory results, when seizures are controlled, show:
Lactate 8mmol/L, pH (venous) 7.30, pCO2 28mm Hg, Bicarbonate 16mmol/L, Base Excess -7.
Secondary causes of lactic acidemia have been excluded.

a) How would you present the laboratory results to an attending physician?
b) Provide a differential diagnosis for this patient. What would be your next steps, with justification?

The results of the laboratory tests you have done suggest PDH complex deficiency.

c) Describe the enzyme involved (structure, cofactors, substrate).

d) Outline with a simple diagram four (4) metabolic pathways (no chemical structures required) for pyruvate catabolism.

e) What is the most common biochemical defect of PDH deficiency outside of the Jewish population

f) Describe the clinical phenotypes associated with the defect listed in e) above. Specify in your answer if there is gender-specific presentation.

g) Describe two (2) treatment options you would recommend as long-term treatment? Explain your rationale.