QADIS

Quick Assessment of Data Interpretation Skills

in

Metabolic Disorders

2016

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Pakistan Society of Chemical Pathologists
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Disclaimer: All efforts have been made to include most recent and reliable information in this book but knowledge and best practice in this field keeps on changing very rapidly. So it is the responsibility of the health practitioners to make decision regarding patient care based on their patient experience and any further update on the subject.

Authors of the booklet declare no conflict of interest of any sort or any nature.

Dedicated to the teacher of the teachers, father of Chemical Pathology in Pakistan and the first FRCPath (Chemical Pathology) in the sub-continent:

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Foreword

In the middle of the day telephone of a Consultant Chemical Pathologist rings. “I am Dr. Akram, Consultant Paediatrician, we have a neonate with …… (Then he narrates all the biochemical findings of the patient and seeks opinion of the Chemical Pathologist). This is a common scenario in many Chemical Pathologists` offices when he/she has to give a candid and quick response on the data of the patient. Keeping this future employment of our postgraduate students in mind, QADIS has been developed. Although data interpretation module is being used in summative assessment (final exam) for more than two decades, it required formatting and standardization. So QADIS is not only new name of this examination tool but is also its characterization and extended application. QADIS is not only an examination tool but also a novel mode of information transfer (MIT). During the year 2015, QADIS was conducted on last Wednesday of each month simultaneously in 13 centers all over the country with a participation of nearly 70 PG students of Chemical Pathology (FCPS, MPhil and MCPS). This was followed by a key presentation with explanation slides along-with supporting literature for the facilitators to use it as an MIT in the class. In some lessons points of further discussion (PFD) were also initiated to increase the depth of knowledge of the students. Our PG students now fully own QADIS and PFDs as learning tool (though many humorous attires have also been created by the students).

QADIS pattern of teaching is also used in routine teaching. So we developed a handsome pool of QADIS cases (we call them patients to avoid the stigmatized term of ‘cases’). PG students all over the country use these cases for learning and revision. The QADIS is an independent module in all practical examinations of Chemical Pathology including MCPS, FCPS and MPhil. We saw these students getting print-outs of the presentations containing the patient data and explanation slides and binding these low qualities photocopies into large binders. So there was a popular demand to publish a ‘QADIS Book’. We took this mammoth task of compiling all the cases along with the relevant explanatory material with references. Another innovation in this compilation is making it a ‘workbook’ rather than a simple description. So each case (patient) data is followed by an appropriate space, so that the students can write the answers based on their existing knowledge, which will become a mean to activate their prior knowledge and build new facts on the rendezvous provided in the form of prior knowledge. At the cost of the extra-volume, we ensured that answers of the questions are on the next page.

A unit QADIS case occupies 2-3 pages of the book. It comprises patient scenario, laboratory data (mostly biochemical), two (occasionally one) short questions, open space for writing likely answers on one page. Next page starts with correct answers, a few lines of explanation and then reference. In some cases, the explanation spreads on two pages and references are more than one.

We have PowerPoint presentations of all these cases divided in chapters exactly like given in this book. The meticulous work of making chapters was done by our senior trainee Dr. Safia Fatima (one of the editors of the book), otherwise the monthly QADIS was not topic-based. Dr Safia has also collected the articles which were provided with the key of monthly QADIS lessons. So we have also topic-wise folders of the reference articles. Dr Lubna Sarfraz converted all the PowerPoint material into word format besides being an important contributor of the cases.

It must be noted that the QADIS cases were contributed by the Consultant Chemical Pathologists of the country, so their names have been included in the 'Contributors'. We are deeply indebted to all these teachers for their value contribution, which will go long way in facilitating teaching and learning Chemical Pathology. With the advent of modular curricula we are sure that our undergraduate students can also benefit from it in their PBL sessions and integrated learning.

In a nutshell this book is an effort to enhance data interpretation competency of our PG and undergraduate students. It is our humble request to all of them to use it honestly as a workbook to gain maximum benefit but please write the answers in the given space in an erasable pencil to do the exercise more than once.

On behalf of all the editors and contributors we will request you to contact us with your valuable inputs to be included in the next editions.

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Contents

Acid Base Disorders

Patient No 1

A 23 years old male is admitted in a hospital with severe diarrhoea but no vomiting probably due to cholera. His biochemical investigations were as following:

- pH 7. 23 (7.35-7.45)
- Base Excess -15.3 (<+3- -3)
- PCO_2 29.1 mmHg (35-45)
- PO_2 97 mmHg (80-100)
- Bicarbonate 14.1 mmol/L (22-28)
- Na 136 mmol/L (138-145)
- K 2.4 mmol/L (3.5-5.0)
- Chloride 106 mmol/L (95-105)
- Anion Gap: 18.3 (8-14)

a. What is the most likely Acid Base Disorder this patient is suffering from?

b. Write two possible causes of raised Anion Gap in this patient.

Write your Answers here

Answers

Patient No 1

a. *Double acidosis; High Anion and Normal Anion Gap Metabolic Acidosis*

b. *Acute Kidney Injury and Lactic Acidosis*

Explanation

a. This is a type of Double Acid Base Disorder
b. The most important feature is presence of hyperchloraemia in a patient with high anion gap (AG).
c. In this disorder delta-ratio (delta/delta) is <1 i.e.:
d. AG-12 / 24 - HCO_3 = <1
e. In our patient (Patient No 1) :

   (18-12) / (24 – 14) = 0.6

f. Patient has severe diarrohea which have led to Acute Kidney Injury or lactic acidosis causing high AG metabolic acidosis in a setting of hyperchloraemic metabolic acidosis

Patient No 2

A 70 years old man presented with persistent vomiting, severe congestive cardiac failure, and moderate renal failure. His biochemical analysis revealed

• pH	7.58		(7.35-7.45)
• PO_2	104	mmHg	(80 – 110)
• PCO_2	25	mmHg	(35-45)
• HCO_3	19	mmol/L	(23 – 33)
• Na^+	142	mmol/L	(132 – 144)
• K^+	5.2	mmol/L	(3.2 – 4.8)
• Cl	99	mmol/L	(98 – 108)
• Anion Gap	29	mmol/L	(7-17)

a. What is the most probable Acid Base Disorder in this patient?

b. Name the biochemical ratio that can be helpful in reaching the diagnosis.

Write your Answers here

Answers

Patient No 2

a. Triple Disorder i.e. Respiratory Alkalosis, Metabolic Acidosis and Metabolic Alkalosis

b. Delta Delta or Delta ratio

Explanation

A. Steps in Diagnosis of a Triple Disorder with Resp Alkalosis

a. Diagnose Double Disorder
b. Examine AG
c. Examine [HCO_3]
d. Example:
e. Double Disorder : Low PCO_2+ High [HCO_3]
   (i.e. Resp Alk + Met Alk)
f. Diagnose Triple Disorder : Low PCO_2+ High [HCO_3] + AG > 16
g. (i.e. Resp Alk + Met Alk+ High AG Met Acidosis)

B. Steps in Diagnosis of a Triple Disorder with Resp Acidosis

Diagnose Double Disorder

a. Examine AG
b. Examine [HCO_3]
c. Example:
d. Double Disorder: High PCO_2+ [HCO_3] higher than the upper limit of compensation
   a. (i.e. Resp Acidosis + Met Alk)
e. Diagnose Triple Disorder: High PCO_2+ [HCO_3] higher than the upper limit of compensation + AG > 16
f. (i.e. Resp Acidosis + Met Alk + High AG Met Acidosis)

Important Notes

a. Respiratory Acidosis and Respiratory Alkalosis never occur together in the same patient !!!

b. The delta ratio is used for the determination of a mixed acid base disorder in an elevated anion gap metabolic acidosis

Measured anion gap – Normal anion gap

Normal [HCO3-] – Measured [HCO3-] or

(anion gap – 12) = (24 - [HCO3-])

Delta Ratio Assessment Guideline

< 0.4	Hyperchloraemic normal anion gap acidosis
0.4 - 0.8	• Renal failure • Combined high AG & normal AG acidosis
1 to 2	• Uncomplicated high-AG acidosis • Lactic acidosis: 1.6 (average value)
>2	A pre-existing elevated HCO3 level due to: – a concurrent metabolic alkalosis, or – a pre-existing compensated respiratory acidosis

Patient No 3

A 74 years old male is critically ill in ICU. His ABG results are as following:

- pH 7. 18 (7.35-7.45)
- Base Excess -6.0 (<+3- -3)
- PCO_2 47.2 (35-45 mm Hg)
- PO_2 102 (80-100 mm Hg)
- Bicarbonate 19.8 (22-28 mmol/L)
- Na 142 (138-145 mm/L)
- K 5.9 (3.5-5 mmol/L)

a. What is your biochemical diagnosis?
b. Name three most important causes of low bicarbonate in this patient

Write your Answers here

Answers

Patient No 3

a. *Metabolic and Respiratory Acidosis*
b. *ESRD, Lactic Acidosis and DKA*

Explanation

This is a type of Double Acid base Disorder. The most important feature is presence of very low pH

Patient No 4

A 29 years old male has been evacuated from a Middle Eastern country with acute onset of severe respiratory illness suggestive of MERS. He is not a known patient of diabetes or renal disease. His biochemical tests show:

- pH 7. 02 (7.35-7.45)
- Base Excess -19.3 (<+3- -3)
- PCO2 78.2 mm Hg (35-45)
- PO2 77 mm Hg (80-100)
- Bicarbonate 12.1 mmol/L (22-28)
- Na 139 mmol/L (138-145)
- K 6.1 mmol/L (3.5-5)
- Chloride 103 mmol/l (95-105)
- -Urea 7.4 mmol/l (2.5-7.7)
- Creatinine 93 µmol/l (50-120)
-

a. What is the most likely biochemical diagnosis?

b. Name a biochemical test which can be helpful to determine the cause of low bicarbonate in this patient

Write your Answers here

Answers

Patient No 4

a. Mixed Respiratory Acidosis and Metabolic Acidosis

b. Blood Lactate

Explanation

a. Middle Eastern Respiratory Syndrome (MERS) is a viral disease endemic in many Arab Countries.

b. Patients of MERS have severe respiratory disease leading to respiratory failure

c. In the scenario, patient has double acidosis, respiratory and metabolic because HCO_3 is low in the face of high PCO_2

d. Hypoxia due to respiratory failure causes anaerobic metabolism and leads to accumulation of lactic acid and low HCO_3

‘One Minute Decoder’ of ABG Reports

Question 1: Acidosis or Alkalosis ?

Look at pH.

i. **Low pH**-----Acidosis

ii. **High pH**----Alkalosis

iii. **Normal pH**--- A normal pH does not rule out existence of an acid base disorder (see below)

Question 2:Primary disorder is Metabolic or Respiratory ??

Examine pH and HCO_3 relationship (For single disorders)

a. If pH and HCO_3change in the same direction primary abnormality is metabolic

Examples:

- in metabolic acidosis both pH and HCO_3 decrease
- in metabolic alkalosis both pH and HCO_3 increase

b. If pH and HCO3 change in the opposite direction primary abnormality is respiratory

Examples:

- in respiratory acidosis pH decreases and HCO_3 increases
- in respiratory alkalosis pH increases and HCO_3 decreases

Question 3: Single or Double disorder ???

(By Decoder or Equations or by Mobile App)

a. If pH is Abnormal

Examine $PCO_2$and HCO_3 relationship

If PCO_2 and HCO_3change in the same direction ----single disorder

If PCO_2 and HCO_3change in the opposite direction –mixed disorder e.g. double acidosis or double alkalosis.

b. <u>If pH is Normal</u>

If PCO_2 and HCO_3change grossly in the same direction ----mixed disorder of opposing type e.g. Metabolic acidosis and Respiratory alkalosis

<u>Normal acid base status</u>

If pH, PCO_2 and HCO_3 all are normal -----normal Acid Base Status

<u>The Equations (Available Softwares /Mobile Apps)</u>

1. <u>Metabolic Acidosis</u>

Expected pCO2 (mmHg) = 1.5 x [HCO3] + 8 (range: +/- 2)

- Maximal compensation may take 12-24 hours to reach
- The **limit of compensation** is a PCO_2 of about 10 mmHg
- Hypoxia can increase the amount of peripheral chemoreceptor stimulation

Example: A patient with a metabolic acidosis ([HCO3] 14mmol/l) has an actual PCO_2 of 30 mmHg. The expected PCO_2 is (1.5 x 14 + 8) which is 29 mmHg. This basically matches the actual value of 30 so compensation is maximal and there is no evidence of another respiratory acid-base disorder

2. <u>Metabolic Alkalosis</u>

Expected PCO2 = 40 + ((Measured bicarbonate - 24) x 0.6)

In metabolic alkalosis (alkalemia plus a high plasma[HC03) the compensatory response is hypoventilation and an increase in the blood PCO_2, (respiratory acidosis). Unlike metabolic acidosis, the PCO_2 response in this condition is irregular, but the limit of compensation for PCO2 is about 60mmHg**.**

Example: A patient with a metabolic alkalosis ([HCO_3] 30mmol/l) has an actual PCO_2 of 35mmHg. The expected PCO_2 is (0.9 x 30+ 9) which is 36mmHg. This basically matches the actual value of 36 so compensation is optimal and there is no evidence of another respiratory acid-base disorder

3. <u>Acute Respiratory Acidosis</u>

Expected [HCO_3] = 24 + { (Actual PCO_2 - 40) / 10 }

Example: A patient with an acute respiratory acidosis (PCO_2 60mmHg) has an actual [HCO_3] of 31mmol/l. The expected [HCO_3] for this acute elevation of PCO_2 is 24 + 2 = 26mmol/l. The actual measured value is higher than this indicating that a metabolic alkalosis must also be present.

4. CHRONIC RESPIRATORY ACIDOSIS

EXPECTED [HCO_3] = 24 + 4 { (ACTUAL PCO2 - 40) / 10}

EXAMPLE: A PATIENT WITH A CHRONIC RESPIRATORY ACIDOSIS (PCO2 60MMHG) HAS AN ACTUAL [HCO3] OF 31MMOL/L. THE EXPECTED [HCO3] FOR THIS CHRONIC ELEVATION OF PCO2 IS 24 + 8 = 32MMOL/L. THE ACTUAL MEASURED VALUE IS EXTREMELY CLOSE TO THIS SO RENAL COMPENSATION IS MAXIMAL AND THERE IS NO EVIDENCE INDICATING A SECOND ACID-BASE DISORDER.

5. ACUTE RESPIRATORY ALKALOSIS

EXPECTED [HCO_3] = 24 - 2 { (40 - ACTUAL PCO_2) / 10 }

*EXAMPLE: **A PATIENT WITH AN ACUTE RESPIRATORY ALKALOSIS (PCO2 15 MMHG) HAS AN ACTUAL [HCO_3] OF 13 MMOL/L. THE EXPECTED [HCO_3] FOR THIS CHRONIC ELEVATION OF PCO2 IS 24 - 5 = 19 MMOL/L. THE ACTUAL MEASURED VALUE IS LOWER THAN THIS INDICATING THAT A METABOLIC ACIDOSIS MUST ALSO BE PRESENT***

6. CHRONIC RESPIRATORY ALKALOSIS

EXPECTED [HCO_3] = 24 - 5 { (40 - ACTUAL PCO_2) / 10 } (RANGE: +/- 2)

- It takes 2 to 3 days to reach maximal renal compensation
- The **limit of compensation** is a [HCO_3] of about 12 to 15 mmol/l

EXAMPLE: **A PATIENT WITH CHRONIC RESPIRATORY ALKALOSIS (PCO2 15 MMHG) HAS AN ACTUAL [HCO_3] OF 13 MMOL/L. THE EXPECTED [HCO_3] FOR THIS CHRONIC ELEVATION OF PCO2 IS 24 - 5 = 12 MMOL/L. THE ACTUAL MEASURED VALUE IS CLOSE TO THIS IS SO THERE IS NORMAL RENAL COMPENSATION AND THERE IS NO EVIDENCE INDICATING A SECOND ACID-BASE DISORDER.**

7. DELTA RATIO = (ANION GAP – 12) / (24 - [HCO_3^-])
8. PREDICTED [HCO_3^-] = 24 -[ANION GAP-12]

Adrenal Disorders

Patient No 5

A 29 years old female presented with complaints of fatigue, lethargy and frequent thirst. She has been having episodes of hypotension as well. Her BMI is 23 kg/m^2. Pigmentation is seen in the palmar creases and the buccal mucosa. She has a small diffuse goiter.

Her lab investigations are as follows:

- Plasma Glucose fasting: 15.3 mmol/L
- Serum Na: 123 mmol/L
- Serum K: 6.0 mmol/L
- Serum Ca: 2.38 mmol/L (2.10-2.65)
- Serum Cortisol (0800 h): 2.0 ng/ml (10-25)
- Plasma ACTH (0800 h): 1650 pg/mL (10-50)
- Serum TSH: 38 mIU/L (0.4-4.5)

a. What is the most likely diagnosis?

b. Name two hormones you will like to test in this patient

Write your Answers here

Answers

Patient No 5

a. Polyglandular autoimmune syndrome type II (Schmidt Syndrome)

b. FSH and LH

Explanation

- Polyglandular autoimmune syndrome type I
  - Adrenal insufficiency
  - Hypoparathryoidism
  - Candidiasis
  - Hypogonadism
  - GI disorders
- Polyglandular autoimmune syndrome type II (Schmidt Syndrome)
  - Adrenal insufficiency
  - Hypogonadism, D.M
  - Hypopituitarism, hypothyroidism
  - Other nonendocrine autoimmune disorders
- **Important differentiating points between the two:**
  - No Hypoparathryoidism and Candidiasis in type II

Patient No 6

A 45 years female complains of episodes of headache, sweating, and tachycardia. She also describes that these attacks are accompanied by high blood pressure but there is no documentation. Her BMI is 22 Kg/m^2. Her routine biochemical profile shows:

- Glucose (F): 6.9 mmol/L (<5.6)
- Na: 138 mmol/L (132-144)
- K: 4.6 mmol/L (3.2-4.8)
- Urea: 4.3 mmol/L (3.6-6.7)
- ALT: 29 U/L (< 42)

To further investigate her Impaired Fasting Glucose, she underwent OGTT which showed 2 hours post-challange value as 7.4 mmol/L.

a. What is the most probable diagnosis?

b. Name two tests available in the state-of-the-art laboratories to confirm the diagnosis?

Write your Answers here

Answers

Patient No 6

a. Pheochromocytoma (or Paraganglionoma)
b. Urine Catecholamines and Normetanephrine

Explanation

a. Classic Triad The classic triad of symptoms in patients with a pheochromocytoma consists of episodic headache, sweating, and tachycardia. About half have paroxysmal hypertension
b. Urine Tests: Diagnosis of these tumours are made if one or more of following urine tests are positive:

- Norepinephrine >170 mcg/24 hour; Epinephrine >35 mcg/24 hour
- Dopamine >700 mcg/24 hour;
  Normetanephrine >900 mcg/24 hour or metanephrine >400 mcg/24 hour

Differentiating Pheochromocytoma and Paraganglionoma

a. Plasma Tests: Plasma fractionated metanephrines is now recommended by some recent studies. These tests carried out on LC/MS/MS have high sensitivity and negative predictive value
b. Pheochromocytomas and paragangliomas are neuroendocrine tumors arising from adrenal and extraadrenal chromaffin cells, respectively.
c. Adrenal tumors (50%) produce a mixture of norepinephrine and epinephrine and the other half nearly exclusively norepinephrine or in occasional cases norepinephrine and dopamine.
d. In contrast, paragangliomas of the thorax, abdomen, and pelvis rarely produce significant amounts of epinephrine, with most producing solely norepinephrine, others a combination of norepinephrine and dopamine, and some exclusively dopamine.

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1. Pheochromocytoma. www.uptodate.com.2015 UpToDate

2. Clinical Chemistry 60:12 1486–1499 (2014)

Patient No 7

A 48 years female has hypertension, the cause of which is being investigated. Her pulse is 78/min and there are no episodes of tachycardia and sweating. Her biochemical investigations revealed:

- Na 143 mmol/L (138-145)
- K 4.2 mmol/L (3.5 - 5.0)
- Chloride 101 mmol/L (95-105)
- Plasma Aldosterone : 339 pmol/L (272-421)
- Active Renin Mass Concentration (ARC): 21.2 ng/L (10.1 – 12.4)
- Aldosterone: ARC ratio : 38.2 (37.6-41.2)

a. Which type of hypertension she is most probably suffering from?

b. Name the disease which is clearly ruled out as a cause of her hypertension

Write your Answers here

Answers

Patient No 7

a. Essential Hypertension

b. Primary Hyperaldosterone

Explanation[1]

a. Active Renin Mass Concentration (ARC) is a better indicator of Renin as compared to previously used Plasma Renin Activity
b. Aldosterone to Renin (ARR) ratio based on ARC is now used
c. Recommended ARR cut-off for Primary Aldosteronism : > 130pmol/ng
d. Essential Hypertension: < 100 pmol/ng

References

1. François Corbin, Pierre Douville, Marcel Lebel. Active renin mass concentration to determine aldosterone-to-renin ratio in screening for primary aldosteronism. International Journal of Nephrology and Renovascular Disease 2011:4 115–120

Patient No 8

A 4 month old male infant presented with irritability and failure to thrive. On examination, he was having tachycardia, dryness of mucus membranes and decreased skin turgor. His laboratory investigations revealed:

• Plasma Glucose	4.6	mmol/L	
• Serum Creatinine	30	umol/L	(4-29)
• Serum Sodium	121	mmol/L	(136-149)
• Serum Potassium	6.0	mmol/L	(3.5-5.0)
• Serum Bicarbonate	15	mmol/L	(22-28)
• Serum Chloride	99	mmol/L	(98-107)
• Serum 17OH Progesterone	2.2	nmol/L	(0.1-2.7)
• Serum Cortisol	575	nmol/L	(80-580)
• Plasma Aldosterone	56	pmol/L	(140-849)

a. What is the most probable diagnosis?
b. Name the most probable biochemical defect

Write your Answers here

Answers

Patient No 8

a. Congenital Isolated Hypoaldosteronism (Type IV RTA also acceptable)

b. Aldosterone synthase (P450c11as) Deficiency

Explanation[1]

Characterized by:

- Hyperkalaemia
- Hponatraemia (in young children)
- Mild Metabolic Acidosis (hyperchloraemic)

Congenital Isolated Hypoaldosteronism:

In children, hypoaldosteronism can result from a congenital defect e.g. deficiency of aldosterone synthase (P450c11as)

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1. Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA) www.uptodate.com ©2015

Patient No 9

An 18 years old female presented with the complaints of irregular menstruation and hirsuitism. This problem is present for four years but becoming worse for the last one year. Her lab investigations revealed:

- FSH: 21.1 mIU/ml (1.4-9.9)
- LH: 19.3 mIU/ml (1.7-15)
- Prolactin 20 ng/ml (3.8-23.0)
- Testosterone 24.8 ng/dl (0.6-5.0)
- DHEAS 15.3 umol/L (1.2- 11.0)
- 17-hydroxyprogesterone (Basal): 13.0 nmol/L
- 17-hydroxyprogesterone (30 min after synacthen injection): 272 nmol/L
-

a. What is the most probable diagnosis?

b. Give two other differential diagnoses.

Write your Answers here

Answers

Patient No 9

a. Late onset congenital adrenal hyperplasia (CAH)

b. (1) Polycystic Ovary Syndrome (PCOS)

(2) Androgen secreting adrenal tumour

Explanation[1]

a. Interestingly it is more common than 'Classical Variety' (see ref)
b. In this patient basal level of 17-OH progesterone was quite high and indication of Synacthen Test was challenged by some (intelligent!) trainees.
c. In adults it can be done to confirm diagnosis (see ref).
d. However, one really wonders why this girl did not present at an early age but then in medicine and biology such variations do occur.

References

1. Diagnosis and treatment of non-classic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency www.UpToDate.com2015

Patient No 10

An XX female neonates has clitoral enlargement with labial fusion. She has hypertension. Her biochemical picture shows:

- pH: 7.46 (7.35-7.45)
- PCO2: 40 mm Hg (35-45)
- HCO3: 30 mmol/L (23-28)
- PO2: 103 mm Hg (80-110)
- Na : 146 mmol/L (135-150)
- K : 2.2 mmol/L (3.5-5.0)
- Cl : 101 mmol/L (98-106)
- DHEA-S: Raised
- Testosterone: Raised

a. What is the most probable diagnosis?

b. Name two steroid metabolites which are raised in this condition.

Write your Answers here

Answers

Patient No 10

a. 11-B dehydroxylase deficiency

b. 11-deoxycortisol and 11-deoxycorticosterone,

Explanation[1]

a. *CYP11B1* (or 11-beta-hydroxylase) deficiency is the second most common cause of congenital adrenal hyperplasia after 21-Hydroxylase deficiency.

b. **Two Cardinal Presentations:**
   (1) Virilization of female neonate
   (2) Hypertension

c. **Biochemical Findings**: High serum concentrations of 11-deoxycortisol, 11-deoxycorticosterone, and dehydroepiandrosterone sulfate (DHEA sulfate), androstenedione, and testosterone.

References

1. Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency. WWW.UpToDate.com 2015

Patient No 11

A 48 years old male presents in A&E of a hospital with weakness in all four limbs. On examination he was found to be having high blood pressure (185/105 mmHg). He confesses intake of ***malathi (Licorice)*** for the last a few weeks as a medicine.

His lab investigations showed following important findings:

- Serum Sodium : 149 mmol/L (132-144)
- Serum Potassium : 2.6 mmol/L (3.5-5.0)
- Urinary Calcium : 380 mmol/mol of Creat (565)
- Plasma active renin mass conc 3.45 ulu/ml (8-35)
- Plasma aldosterone 1.6 ng/dl (1-16)
- Aldosterone: Renin Ratio: 0.46
- 24 h Urine cortisol : cortisone ratio 0.02

a. What is the most probable diagnosis in this patient?

b. What is the most important biochemical cause of this condition?

Write your Answers here

Answers

Patient No 11

a. Apparent Mineralocorticoid Excess due to licorice ingestion

b. Deficiency of 11betahydroxysteroid dehydrogenase type 2 (11-Beta HSD2)

Explanation[1]

a. The syndrome of apparent mineralocorticoid excess (AME) is characterized by hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity and low plasma aldosterone levels
b. Chronic ingestion of licorice or licorice like compounds (such as carbenoxolone) induces a syndrome with similar findings.
c. The basic defect is inhibition of enzyme 11betahydroxysteroid dehydrogenase type 2 (11-Beta HSD2) which is the renal form of 11-Beta HSD).
d. Points for Further Discussion:
    a. One can differentiate genetic cause of AME from licorice by clinical interview of the patient, otherwise urinary cortisol to cortisone ratio can be helpful. In licorice ingestion it is markedly raised.
    b. AME can be differentiated from Primary Hyperaldosteronism by Plasma Aldosterone levels. It is marked raised in Primary Hyperaldosteronism while low in AME.

References

1. Apparent mineralocorticoid excess syndromes (including chronic licorice ingestion) WWW.UpToDate.com 2015

Patient No 12

A newborn was noted to have bilaterally palpable testes and Grade IV hypospadias in a Children Hospital of USA. There was no other clinical abnormality found. His karyotyping showed XY chromosome while results of steroids were as following:

- 17-Hydroxyprogesterone: Markedly raised
- 17-Hydroxypregnenolone : Markedly raised
- DHEA-S: Raised
- Testosterone after HCG stimulation test: 196 ng/ml (Normal response: 980)

a. What is the most probable diagnosis?

b. Name the enzyme which is most likely deficient in this neonate.

Write your Answers here

Answers

Patient No 12

a. CAH

b. 3 Beta Hydroxysteroid dehydrogenase (3 Beta HSD)

Explanation[1]

a. A rare form CAH (consultants are mainly required for rare diseases!!)
b. It can present as ambiguous genitalia in both XX and XY neonate
c. Sub-optimal response to HCG stimulation test rules out AIS.
d. 3 Beta HSD is an adrenal enzyme while 3 Beta HSD2 is a renal enzyme
e. 3 beta HSD is required for the normal synthesis of adrenal hormones proximal to the enzyme 21 hydroxylase.
f. This result in marked elevation of 17-Hydroxypregnenolone.
g. 11-deoxicortisol remains normal

References

1. Elevated 17 Hydroxyprogesterone and Testosterone in a newborn with 3 Beta Hydroxysteroid dehydrogenase deficiency. NEJM1985; 313(10):618-621

Patient No 13

A 50 years old female was admitted in hospital with two weeks history of generalized weakness and feeling of being unwell. On examination she had hypertension (180/90), generalized edema, hepatomegaly, widespread skin pigmentation and scaly red plaques on her back and legs. Her lab investigations revealed:

- Serum sodium : 147 mmol/l (132-150)
- Serum potassium : 2.1 mmol/l (3.5-5.0)
- Serum creatinine : 110 µmol/l (60-120)
- Plasma glucose (F) : 16.4 mmol/l (3.3-5.5)
- Serum cortisol : > 1600 nmol/l (140-690)
- Serum ACTH : 45.4 pmol/L (4.4 to 11.3)
- High dose Dexamethasone suppression test was done:

Date	Time (h)	Serum cortisol (nmol/l)
26/8	0800	1580
26/8	2300	-8.0 mg Dexamethasone dose given
27/8	0800	1570

a. What is probable diagnosis?

b. Name TWO causes of this condition

Write your Answers here

P

Answers

Patient No 13

a. Cushing syndrome due to ectopic ACTH secreting tumors[1]

b. Tumors of lung, pancreas, colon

Explanation

Please see next Patient

Frequency of causes of Cushing's syndrome

Diagnosis	Percent of patients
ACTH-dependent Cushing's syndrome	
Cushing's disease	68
Ectopic ACTH syndrome	12
Ectopic CRH syndrome	<<1
ACTH-independent Cushing's syndrome	
Adrenal adenoma	10
Adrenal carcinoma	8
Micronodular hyperplasia	1
Macronodular hyperplasia	<<1
Pseudo-Cushing's syndrome	
Major depressive disorder	1
Alcoholism	<<1

Relative prevalence of various causes of Cushing's syndrome in 630 patients (146 consecutive patients seen at Vanderbilt University Medical Center before 1993 and published reports describing 484 patients). The prevalence of pseudo-Cushing's syndrome depends upon the individual clinician's threshold of clinical suspicion; in our experience, it is very rare. The relative prevalence of various causes of Cushing's syndrome among children and adolescents may differ somewhat from that of adults. The ectopic ACTH syndrome, for example, is less common in children.

ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone.

References

1. Establishing the cause of Cushing's syndrome WWW.UpToDate.com 2015

Patient No 14

A 41 years old male underwent bilateral adrenalectomy for Cushing Syndrome. He was taking glucocorticoid replacement therapy but after two years he developed headaches, visual field defects, and pigmentation on wide areas of the body. His hormonal profile revealed:

- Plasma ACTH Level (11 pm): 3420 pmol/L (1.1- 4.4)

a. What is most probable diagnosis?

b. What is the most likely cause of pigmentation in this patient?

Write your Answers here

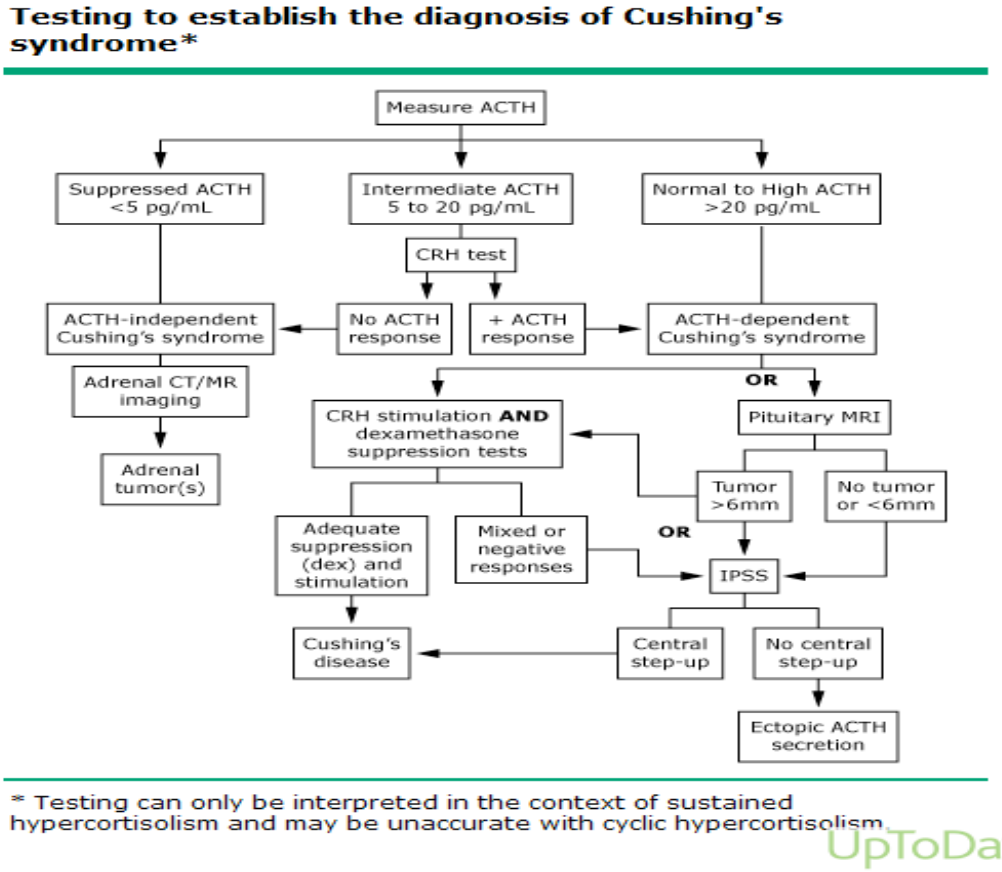
Answers

Patient No 14

a. Nelson Syndrome

b. Excess ACTH secretion

Explanation[1]



References

1. Nelson Syndrome: Background, Pathophysiology, Epidemiology www Medscape.com 2015

Patient No 15

A 32 years old female presented with hirsutism and amenorrhea and weight gain. Her lab investigations showed:

- Plasma testosterone: 7.7 nmol/L (0.9-3.6)
- DHEAS: 13.6 µmol/L (1.2-11.0)
- 24 h urinary free cortisol: 1740 nmol/L (<300)

a. What is the most probable diagnosis?

b. Name ONE further investigation you will like to carry out in this patient

Write your Answers here

Answers

Patient No 15

a. Adrenal Tumour
b. High Dose Dexamethasone test

Explanation[1]

a. In addition to the raised cortisol and low ACTH, most of the adrenal androgens are also raised e.g. testosterone, DHEA-S, androstenedione, and 17-OH progesterone
b. Adrenal carcinomas are notorious in producing hormone precursors in plasma and urine of the patient, which can be detected by using instrument like GC/MS e.g. pregnenediol and pregnenetriol

References

1. Clinical presentation and evaluation of adrenocortical tumours www.UpToDate.com

Patient No 16

An 18 years old female presents in A&E of a hospital with weakness in all four limbs. On examination her blood pressure was 185/105 mmHg. Her brother aged 16 years is also hypertensive. Her lab investigations were

- Na 143 mmol/L (138-145)
- K 2.9 mmol/L (3.5 - 5.0)
- Chloride 93 mmol/L (95-105)
- Bicarbonate 36 mmol/L (23_33)
- Plasma aldosterone 2.1 ng/dl (3-16)
- Active Renin Mass

  Concentration (ARC): 3.8 mIU/L (8-35)

a. What is the likely diagnosis?

b. What is basic underlying defect?

Write your Answers here

Answers

Patient No 16

a. Liddle´s syndrome (or Apparent Mineralocorticoid Excess)

b. Caused by hyperactivity of the epithelial sodium channel or ameloride sensitive sodium channels (ENaC) of the cortical collecting tubule

Explanation[1]

a. Liddle syndrome is characterized by:
   Hypertension in young age
   i. Hypokalaemia
   ii. Low renin and aldosterone
b. It is a 'gain of function' mutation in the gene encoding ENaC of the collecting tubule resulting in autonomous function of these channel without the influence of aldosterone
c. Can be differentiated from Primary Hyperaldosteronism by normal Na level and low aldosterone and renin
d. AME has almost similar presenting features as Liddle i.e. Hypertension in young age, Hypokalaemia and Low renin and aldosterone
e. In AME, the ratio of cortisol to cortisone in urine is 5 while it is normal in Liddle (0.3 to 0.5)
f. Two other important differential diagnosis of AME can be:
   a. Licorice ingestion
   b. Ectopic ACTH syndrome

References

1. Genetic disorders of the collecting tubule sodium channel: Liddle's syndrome and pseudohypoaldosteronism type 1 www.UpToDate.com

Patient No 17

A 2 months old male infant presented with failure to thrive. On clinical examination, he had tachycardia and dehydration. His biochemical investigations showed:

- Plasma Glucose 4.9 mmol/L
- Serum creatinine 28 umol/L (4-29)
- Serum Sodium 124 mmol/L (136-149)
- Serum Potassium 5.9 mmol/L (3.5-5.0)
- Serum Bicarbonate 17 mmol/L (22-28)
- Serum Chloride 101 mmol/L (98-108)
- Serum Cortisol 545 nmol/L (80-580)
- Plasma Aldosterone 980 pmol/L (140-849)
- Plasma active renin mass conc 45 ulu/ml (8-35)

a. What is the most probable diagnosis?

b. Name the most probable biochemical defect

Write your Answers here

Answers

Patient No 17

a. Pseudohypoaldosteronism type 1

b. Mutations in mineralocorticoid receptor or epithelial sodium channel

Explanation[1]

a. It is a rare disorder with aldosterone receptors defect
b. Decreased function of Epithelial Na Channel (ENaC) is the major defect.
c. It is in contrast to Liddle syndrome which is due to increased function of ENaC.
d. Affected child may present with hyperkalaemia, sodium wasting, hypervolemia and metabolic acidosis.
e. May be autosomal recessive or dominant varieties
f. Main differentiating features from type IV RTA is raised plasma aldosterone, while type IV RTA encompasses conditions with hypoaldosteronism

References

1. Genetic disorders of the collecting tubule sodium channel: Liddle's syndrome and pseudohypoaldosteronism type 1. www.UpToDate.com 2015

Patient No 18

A 76-year-old woman was admitted to a geriatric ward for assessment. She was not on any medication and there was no suggestion of diabetes mellitus. Plasma and urinary electrolyte estimation revealed:

- pH: 7.32
- HCO_3 20 mmol/L (23 – 33)
- Na^+ 134 mmol/L (132 – 144)
- K^+ 6.2 mmol/L (3.2 – 4.8)
- Cl 112 mmol/L (98 – 108)
- Creatinine 230 µmol/L (60-120)
- Urea 9.5 mmol/L (3.0-8.0)
- Anion Gap 8 mmol/L (7-17)
- Renin activity 0.1 ng/mL/h (0.1-0.4)
- Aldosterone 4.5 ng/L (10-150)

a. What is the most probable diagnosis?

b. Write TWO causes of this disorder

Write your Answers here

Answers

Patient No 18

a. Type IV RTA

b. Hyporeninaemic Hypo aldosterone and Diabetes mellitus

Explanation[1]

a. RTA type IV is characterized by metabolic acidosis and hyperkalaemia (as opposed to hypokalaemia in other types)
b. Causes:
c. Hyporeninemic Hypoaldosteronism
d. Diabetic nephropathy
e. NSAIDS
f. Calcineurin inhibitors
g. ACE inhibitors and ARBs
h. Heparin and LMW heparin
i. Adrenal insufficiency

References

1. www.UpToDate.com 2015

Patient No 19

A 4 month old male infant presented with irritability and failure to thrive. On examination, he was having tachycardia, dryness of mucus membranes and decreased skin turgor. His laboratory investigations revealed:

• Plasma Glucose	4.6 mmol/L	
• Serum creatinine	30 umol/L	(4-29)
• Serum Sodium	121 mmol/L	(136-149)
• Serum Potassium	6.0 mmol/L	(3.5-5.0)
• Serum Bicarbonate	15 mmol/L	(22-28)
• Serum Chloride	99 mmol/L	(98-107)
• Serum 17OH progesterone	2.2 nmol/L	(0.1-2.7)
• Serum Cortisol	575 nmol/L	(80-580)
• Plasma Aldosterone	56 pmol/L	(140-849)

a. What is the most probable diagnosis?

b. Name the most probable biochemical defect

Write your Answers here

Disorders Affecting
Renin Angiotensin Aldosterone System (RAAS)

Disorders	Aetiology	Secondary Hypertension	Serum Na	Serum K	Acid Base Status	Plasma Aldosterone	Plasma Renin Mass Conc
Barter / Gittleman	NaCl Transporter defect	Absent	Normal	Low	Met. Alkalosis	Raised	Raised
Primary Hyperaldosteronism	Adrenal Disorder	Present	High / Normal	Low	Met Alkalosis	Raised	Low
Apparent Mineralocorticoid Excess	11 Beta* Hydroxysteroid Dehydrogenase def	Present	High / Normal	Low	Met Alkalosis	Low	Low
Liddle Syndrome	Gain of Function of ENaC	Present	High /Normal	Low	Met Alkalosis	Low	Low
Psuedohypoa-dosteronism I	Loss of Function of ENaC	Absent	Low / Normal	Raised	Met Acidosis	High	High
Psuedohypoal-dosteronism II (Gordon Syndrome)	WNK1 & WNK4 Mutations	Present	High/ Normal	Raised	Met Acidosis	Low or inappropriately normal in the face of hyperkalaemia	Low

Answers

Patient No 19

a. Congenital Isolated Hypoaldosteronism (Type IV RTA also acceptable)

b. Aldosterone synthase (P450c11as) Deficiency

Explanation[1]

Characterized by:

- Hyperkalaemia
- Hyponatraemia (in young children)
- Mild Metabolic Acidosis (hyperchloraemic)

Congenital Isolated Hypoaldosteronism:

In children, hypoaldosteronism can result from a congenital defect e.g. deficiency of aldosterone synthase (P450c11as)

References

1. Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA) www.UpToDate.com 2015

Patient No 20

A 7 years old male reported in an Endocrine Clinic with early appearance of secondary sexual characteristics, facial, axillary and pubic hair, phallic enlargement, voice change and rapid increase in height. His ***Hormonal investigation*** revealed:

• TSH	2.96	mIU/L	(0.4- 4.0)
• Cortisol (0800 h)	190	nmol/L	(138-690)
• ACTH (0800 h)	499	pg/ml	(10.0-85.0)
• LH	< 0.07	mIU/ml	(1.0-3.5l)
• FSH	<1	mIU/ml	(0.0- 5.0)
• 17 Hydroxy Progesterone	4.95	ng/ml	(0.03-0.90)
• Testosterone	222	ng/dl	(3.0 -30.0)

a. Name the most probable cause of ***precocious puberty*** in this patient.

b. Write TWO more causes of similar clinical condition in boys of this age group (ignoring hormonal results).

Write your Answers here

Answers

Patient No 20

a. CAH due to 21 hydroxylase deficiency (Both classical and non-classical)

b. Central variety and CNS diseases

Explanation[1]

a. Precocious puberty in this patient is due to 21 hydroxylase deficiency
b. In males, difficult to differentiate between 'Classical' and 'Late-onset'.
c. Other causes include:
    a. Central due to brain lesions
    b. Pituitary
    c. Adrenal

References

1. Genetics and clinical presentation of nonclassic (late onset) congenital adrenal hyperplasia due to 21 hydroxylase deficiency www.UpToDate.com 2015

Patient No 21

A 21 years old male was diagnosed to be a case of Addison`s Disease on the basis of clinical features and laboratory findings (i.e. low cortisol and increased ACTH). He is on replacement therapy and clinically much improved but his recent hormonal profile indicates:

- Cortisol : < 5 nmol/L
- ACTH: 87 pg/ml < 120

a. What is the most probable cause of this discrepancy (analytical error excluded)?

b. What advice you will like to give to the treating physician?

Write your Answers here

Answers

Patient No 21

a. Patient is on prednisolone or dexamethasone which do not cross react with cortisol

b. As a short term treatment patient may be treated with hydrocortisone and monitored with cortisol

References

1. Treatment of Adrenal insufficiency in Adults. www.uptodate.com ©2015

Patient No 22

A 55 years old female is being investigated for Cushing Syndrome. She has following lab results:

- Serum Cortisol in overnight 1 mg dexamethasone suppression test:
  35 nmol/L (Normal Cut-off value: <50 nmol/L)
- Urine free cortisol: 230 nmol/day (ref range: 27 to 150)
- Write two causes of this discrepancy. (Please note that altered CBG and 'Pseudo-Cushing's Syndrome' have already been ruled out in this patient)

a. Name the third First Line Test you will like to carry out in this patient.
b. What advice you will like to give to the treating physician?

Write your Answers here

Answers

Patient No 22

a. Inappropriate urinary output and local (Vaginal)hydrocortisone treatment

b. Late evening salivary cortisol

References

1. Establishing the diagnosis of Cushing Syndrome. www.uptodate.com ©2015

Patient No 23

A 6 years old patient presented in an Endocrine Clinic with labial fusion but absent testes. Patient had dark pigmentation and grown-up beard on the face. Height of the patient was at 93rd percentile.

Lab investigations revealed:

- Karyotyping: 46 XX
- 17 Hydroxyprogesterone: 46.2 nmol/L (0.5-7.2)
- Serum Cortisol (0800 h): 187 nmol/L (138-634)
- Plasma ACTH: 87 pmol/L (<26)
-

a. What is the most probable diagnosis?
b. Write the exact biochemical defect

Write your Answers here

Answers

Patient No 23

a. Heterosexual precocious puberty

b. CAH due to 21-hydroxylase deficiency

Explanation[1]

a. Precocious Puberty is a manifestation of CAH in male.
b. In XX persons CAH presents as ambiguous genitalia
c. But in some XX the genitalia may appear normal and the diagnosis is missed at this age.
d. In later age these patients may present with signs of excessive androgens i.e. excessive facial hair and other male features
e. High ACTH keeps cortisol within reference limits by enlarging the adrenals
f. High ACTH may cause pigmentation

References

1. Precocious Puberty- Book Chapter

https://www.glowm.com/resources/glowm/cd/pages/v5/v5c016.html.

Blood Disorders

Patient No 24

A 24 years old female underwent abortion but she developed certain complications and was shifted to intensive care unit. Her laboratory investigations revealed:-

- ALT: 96 U/L
- PT: Normal: 14 sec
  Patient: 40 sec
- PTTK: Normal: 32 sec
  Patient: 90 sec
- FDP: > 500 ng/L
- D-Dimers: < 250 ng/L

She was given 6 units of FFP but Coagulation Profile did not improve.

a. What is your diagnosis?

b. What treatment you will suggest for this patient?

Write your Answers here

Answers

Patient No 24

a. Disseminated Intravascular Coagulation (DIC)

b. Cryoprecipitate

Explanation[1]

a. DIC is seen in approximately 1 percent of admissions to tertiary care hospitals.
b. DIC is a multi-organ disease requiring expertise of multi-specialty team
c. Chemical Pathologist often has to be the part of this team managing DIC.
d. The hallmark of DIC is coagulation and fibrinolysis occurring side by side but massively.
e. The process of coagulation overtakes the clotting factors synthesis process leading to so called ***'consumption coagulopathy'***.
f. Massive fibrinolysis leads to formation of fibrin which form an important impediment in clotting.
g. Fibrin strands also cause fragmentation of RBC (Shistocytes & helmet cells) by 'guilloting' the RBCs
h. The term 'chronic DIC' is used for mild DIC without clotting defect and thrombocytopaenia.

References

1. Clinical features, diagnosis, and treatment of disseminated intravascular coagulation in adults. WWW.UpToDate.com 2015

Patient No 25

A 22 years male presented with fever and splenomegaly. His laboratory investigations revealed:

- ALT: 234 U/L
- Bilirubin: 92 µmol/L
- Ferritin: >10,000 ng/ml
- Triglycerides: 5.6 mmol/L (<1.35)
- Hb: 7.9 g/L
- TLC: 0.9×10^9 /L
- Bone Marrow Aspiration biopsy: Haemophagocytosis with Histiocytosis seen.

a. What is most likely diagnosis?

b. Name ONE laboratory test which can be used for screening and diagnosis of this disease

Write your Answers here

Answers

Patient No 25

a. Hemophagocytic lymphohistiocytosis (HLH)

b. Soluble CD25 (soluble IL-2 receptor)

Explanation[1]

Salient Features of HLH

a. Fasting hypertriglyceridemia ≥ 3 mmol/L
b. Hypofibrinogenemia ≤ 150 mg/100 ml
c. Ferritin ≥ 500 ug/ml
d. Haemophagocytosis- bone marrow, spleen or lymph nodes
e. Low/absent natural killer cell activity
f. Soluble CD25 (soluble IL-2 receptor) >2400 U/ml
g. No malignancy
h. Ferritin level >500 ug/L: 80-100 percent specific
i. Ferritin concentrations >10,000 ug/L: 90 % sensitive, 96 % specific
j. Identification of pathologic mutations PRF1, UNC13D, or STX11
k. Fever 38.5 ^{0}C
l. Splenomegaly > 3 cm
m. Cytopenias affecting at least two cell lines :
n. Haemoglobin <9 g/100 ml
o. Platelets <100×10^{9}/L
p. Neutrophils <1×10^{9}/L

References

1. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis

WWW.UpToDate.com 2015

Patient No 26

A 27 years old female presented in an A& E Department with acute onset of anuria, nausea, abdominal pain, diarrhea, leading to confusion and lethargy. House officer dug out the history of intake of “Energy Drink” containing quinine.

Her salient laboratory findings were:

- Serum Creatinine: 387 µmol/L
- LD: 987 U/L (122-386)
- Indirect Bilirubin: 88 µmol/L
- Low Platelet count
- Shistocytosis on peripheral blood film

a. What is the most probable diagnosis?

b. Name the test for which you will like to collect blood sample before starting emergency treatment

Write your Answers here

Answers

Patient No 26

a. Haemolytic Uraemic Syndrome

b. ADAMTS13 activity

Explanation[1]

Thrombotic Thrombocytopenic PurpuraHaemolytic Uraemic Syndrome (TTP_UHS)

a. This is another example of multi-organ disease requiring multi-specialty team including Chemical Pathologist
b. There are FIVE components featuring this condition called ***'Pentad'***:
    - ✓ Microangiopathic Haemolytic Anaemia
    - ✓ Thrombocytopaenia
    - ✓ Renal Impairment / AKI
    - ✓ Neurological symptoms e.g. confusion or coma
    - ✓ Fever
c. All five features are present in only 3% of patients
d. It's a spectrum of condition with haemolysis and thrombocytopaenia on one end and renal and neurological involvement on the other.
e. Acquired autoimmune TTP: Caused by autoantibody inhibition of ADAMTS 13
f. Drug-induced thrombotic microangiopathy
g. Quinine is the most common cause.
h. Cancer chemotherapy (mitomycin C, gemcitabine, possibly others)
i. Immunosuppressive agents (cyclosporine, tacrolimus, sirolimus)
j. Bloody diarrhoea caused by *E. coli* or *Shigella* species
k. Pregnancy or postpartum:.
l. Hereditary TTP
m. Autoimmune disorders

References

1. Diagnosis of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults WWW.UpToDate.com 2015

Patient No 27

A 74 years old man complains of muscle pain, weakness, fever, nausea, vomiting and dark urine for the last one hour. His biochemical profile revealed:

- CK 7705 U/L
- Aldolase 657 U/L
- The urine dipstick test for blood: POSITIVE
- Urine Microscopy: No red blood cells are seen

a. What is the most likely diagnosis?

b. Why urine dipstick test is positive for blood when RBCs are not seen on microscopy?

Write your Answers here

Answers

Patient No 27

a. Rhabdomyolysis (acute)

b. Myoglobin in urine reacts positive in dipstick test

Explanation[1]

a. Very high CK i.e. 1500 to 100,000 U/L: Mainly CK-MM but some quantity of CK-MB is also present which also comes from skeletal muscles
b. Myoglobinuria: it has very short have life and is converted to bilirubin. It persists in blood for shorter period than CK.
c. Raised ALT and AST
d. Hypovolemia due to shifting of fluid to injured muscles
e. Hyperkalaemia
f. Hyperphosphataemia

References

1. Clinical manifestations and diagnosis of rhabdomyolysis www.UpToDate.com 2015

Calcium and Bone Metabolism

Patient No 28

A 41 years old female was hospitalized in the Oncology Clinic. The patient had four spontaneous fractures (foot, clavicle, upper arm, forearm) four years ago. She also reported poor appetite, nausea and vomiting every day during the last several months.

Her biochemical profile is as following:

- Na: 141 mmol/L (132-144)
- K: 2.4 mmol/L (3.2-4.8)
- Urea: 4.3 mmol/L (3.6-6.7)
- Ca: 3.84 mmol/L (2.1-2.65)
- P: 0.81 mmol/L (0.81-1.45)
- Alkaline Phosphatase: 205 U/L (24-125)

a. What is the most important diagnosis in this patient?

b. Name ONE lab test you should advise to confirm your diagnosis?

Write your Answers here

Answers

Patient No 28

a. Primary Hyperparathyroidism (Hypercalcaemia of Malignancy is also acceptable diagnosis)
b. PTH

Explanation[1]

a. Increased Calcium and Low Phosphate are strong indicators of Primary Hyperparathyroidism and Hypercalcaeima of Malignancy
b. In this patient clinical scenario favours parathyroid etiology because of relatively longer history and involvement of other systems but this diagnosis cannot be reached just by Biochemical data. So malignancy is also an acceptable diagnosis.
c. PTH (i.e. Plasma iPTH) will be a very good test to differentiate these two conditions.
d. In malignancy it will be undetectable or very low

References

1. Marshal Clinical Cases.

Patient No 29

A 50 years old male complained of mechanical back and knee pains of a few years duration. On examination, there was mild restriction of the lumbosacral spine movement and patello-femoral crepitus. There was mild bone tenderness, too.

His biochemical investigations were as following:

- Ca: 2.34 mmol/L (2.1-2.65)
- P: 0.81 mmol/L (0.81-1.45)
- Alkaline Phosphatase: 835 U/L (24-125)
- Serum 25-OH-D3 : 35 ng/ml (30 – 150)
- PTH : 43 pg/ml (15 – 65)

a. What is the most probable diagnosis?

b. Name THREE further laboratory investigations will you order to confirm your diagnosis?

Write your Answers here

Answers

Patient No 29

a. Paget`s Disease of the bones

b. (1) Bone Specific ALP,

(2) Procollagen type I N-terminal Propeptide (PINP)

(3) Serum Ctelopeptide (CTx)

(4) Urinary Ntelopeptide (NTx)

(5) Urinary hydroxyproline

Explanation[1]

a. One of the most common diseases of the bones
b. Prevalence is upto 9% in some European countries
c. Usually asymptomatic
d. Bone pain and bone overgrowth are common symptoms in aging population
e. High Serum Alkaline Phosphatase (ALP) is the hallmark of the disease
f. If bone ALP is not available, liver origin can be ruled out by carrying out gamma GT.
g. Bone turn-over markers are also elevated

References

1. Clinical manifestations and diagnosis of Paget disease of bone
www.uptodate.com ©2015 UpToDate

Patient No 30

A 70 year old female visits a geriatric clinic for routine evaluation. She is rather short and has mildly low IQ. She has had lifelong hypocalcaemia and hyperphosphatemia. Recent values are:

- Serum calcium : 5.2 mg/dl (8.4 – 10.2)
- Serum phosphorus : 6.2 mg/dl (2.5 – 4.5)
- Serum Urea: 32 mg/dl (18-38)
- Serum 25-OH D3 : 30 ng/ml (15 – 60)
- PTH : 130 pg/ml (15 – 65)

1. What is the most probable diagnosis in this case?
2. Name any THREE subtypes of the disease

Write your Answers here

Answers

Patient No 30

a. Pseudohypoparathyroidism

b. Type Ia, Type Ib and Type Ic

Explanation[1]

a. Can occur at any age from infancy to senescence
b. Biochemical Characteristics
    a. Hypocalcaemia
    b. Hyperphosphataemia
    c. High PTH
c. Types
    a. Type 1a
    b. Type 1b
        i. Type 1c
        ii. Type 2

References

1. Etiology of hypocalcemia in infants and children www.uptodate.com 2015

Patient No 31

An 11 years old boy was being investigated for incidental finding of hypercalcemia. His lab results revealed:

Serum Calcium:	3.12 mmol/L	(2.1 -2.6)
Serum Phosphate:	1.24 mmol/L	(0.8 -1.4)
Serum Magnesium:	1.1 mmol/L	(0.6 – 1.0)
Plasma PTH:	55 ng/L	(10-65)
25 OH Vit D:	94 nmol/L	(Normal: >75)

Calcium Creatinine clearance ratio: < 0.01.

a. What is the most probable diagnosis?
b. What is the basic molecular defect?

Write your Answers here

Answers

Patient No 31

a. Hypocalciuric Hypercalcaemia

b. Calcium Sensing Receptors defect

Explanation[1]

a. It is a 'loss of function mutation in 'Calcium Sensing Receptor' (CaSR) gene.
b. In neonates the disease may present with ' Neonatal Severe Primary Hyperparathyroidism ' (NSHPT)
c. The degree of hypercalcemia in these two disorders reflects a gene dose effect.
d. FHH heterozygotes have mild hypercalcemia because of partial loss of CaSR.
e. In contrast patient who are homozygous for the CaSR gene defect have more marked disease i.e. NSHPT

References

1. Familial hypocalciuric hypercalcemia. www,uptodate.com 2015

Patient No 32

A one month old child is failing to thrive and unwell. His biochemical profile shows:

- Serum Calcium: 3.21 mmol/L (2.1-2.65)
- Serum Phosphorous: 0.81 mmol/L
- Alkaline Phosphatase: 118 U/L (24-125)
- Serum $1,25(OH)_2D3$: 55 ng/ml (30 – 150)
- PTH : 125 pg/ml (15 – 65)
- Urea 3.9 mmol/L (3.1-6.4)
- Creatinine 47 µmol/L (56-82)
- Urine Ca / Creatinine Clearance Ratio: 0.008 (Normal > 0.01)

a. What is the most probable diagnosis?

b. Name the genetic abnormality present in this condition.

Write your Answers here

Answers

Patient No 32

a. Neonatal Severe Primary Hyperparathyroidism

b. Calcium Sensing Receptor (CaSR) gene defect (homozygous variety)

Explanation[1]

Loss of Function Mutation:

The inactivating mutations of the CaSR in FHH make the parathyroid glands less sensitive to calcium. A higher than normal serum calcium concentration is required to reduce PTH release

Familial Hypocalciureic Hypercalcaemia (FHH): This is a heterozygous variety with:

(1) Mild Hypocalcaemia in childhood
(2) Normal PTH
(3) High Mg
(4) Urine Ca : Creatinine Clearance < 0.01

Loss of Function Mutation:

Neonatal Severe Primary Hyperparathyroidism (NSPH): This is homozygous variety:

(1) Severe Hypercalcaemia in childhood
(2) High PTH
(3) High Mg
(4) Urine Ca : Creatinine Clearance < 0.01

Gain of Function Mutation: Autosomal Dominent Hypoparathyroism

(1) This is due to shifting of Ca-PTH curve to the left, so the Ca level goes very low before a PTH response can ensue.
(2) Hypocalcaemia
(3) Inappropriately normal PTH
(4) High Phosphorous

References

1. Disorders of the calcium sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant Hypocalcaemia www.uptodate.com ©2015

Patient No 33

A 47 years old male had cough, dyspnoea and mild chest pain. His radiological examination of chest revealed diffuse interstitial lung disease and bilateral hilar adenopathy. His laboratory findings were:

- Haemoglobin: 11.2 g/dl
- ESR: 31 mm at the end of first hour
- Calcium: 2.85 mmol/L (2.10 – 2.65)
- Phosphorus: 1.15 mmol/L (0.81-1.45)
- ALP: 234 U/L (30 – 120)
- ACE: 178 U/L (8-53)

a. What is the most probable diagnosis?

b. Which metabolite of Vitamin D will be most helpful to confirm the diagnosis?

Write your Answers here

Answers

Patient No 33

a. Sarcoidosis

b. Elevated 1, 25-dihydroxyvitamin D

Explanation[1,2]

1. Hypercalcaemia
2. Hypercalciuria is also quite common
3. Raised Alkaline phosphatase
4. Hypergammaglobulinaemia
5. Raised Angiotensin Converting Enzyme (ACE)
6. Elevated 1, 25-dihydroxyvitamin D

References

1. Clinical Manifestation and Diagnosis of Sarcoidosis. WWW. UpToDate.com
2. Kavathia D, Buckley JD, Rao D, Rybicki B, Burke R. Elevated 1, 25- dihydroxyvitamin D levels are associated with protracted treatment in sarcoidosis. Respiratory Medicine (2010) 104, 564 - 570

Cardiac Biomarkers

Patient No 34

A 50 years old male was admitted in a hospital with retrosternal chest pain of 6 hours duration. His body temperature, pulse rate, and blood pressure were 38.2 °C, 115 beats/min, and 80/40 mmHg, respectively. Electrocardiography was suggestive of Acute Coronary Syndrome. Investigations showed:

- Cardiac Troponin I: 0.3 ng/ml (99^{th} percentile 0.1 ng/ml)
- Echocardiography showed a Hypokinetic area

a. What advise you will give regarding Cardiac Troponin I Assay?

b. Name a more advanced technical version of Cardiac Troponin I that can be used in this patient for better clinical results?

Write your Answers here

Answers

Patient No 34

a. Repeat Troponin I after 6 hours to document rise and fall.

b. Highly sensitive Troponin I (hs Troponin I).

Explanation[1,2]

Third Universal Definition of Myocardial Infarction (2012)

a. MI has been redefined by consensus of many international organization.
b. A lot of emphasis is given to Troponin Assay now
c. In the next two slides you will find some salient features of this definition from the original article

Points For Further Discussion

a. Why demonstration of ***'Rise and Fall'*** of troponins is essential for the diagnosis of Myocardial Infarction (MI)
   Answers: To rule other cardiac causes such as myocarditis
b. Name ONE major issue of Standard Troponin assays related to the sensitivity which has been overcome in hs Troponin assay
   Answers: It cannot differentiate normal levels
c. What is the criteria of declaring a troponin assay "High Sensitive' or hs Troponin Assay?
   Answers: Low Level of Quantification (LOQ)
d. Is it appropriate to carry out CK-MB or CK-MB (mass) if hs Troponin assay is available in a lab.
   Answers: No. It should not be carried out.

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

References

1. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin assays. N Engl J Med 2009;361:858-67.
2. ***http://circ.ahajournals.org/content/126/16/2020***

Patient No 35

(Recent Updates)

A 52 years old male is admitted in an A& E of a state-of-the-art hospital with chest pain of three hours duration. His cardiac markers carried out on admission showed:

- Serum CK-MB (Mass): 3.7 ng/ml (< 4.9)
- Serum Troponin I (HS) : 0.021 µg/L (99^{th} % 0.04)
- Serum Myoglobin: 149 µg/L (0 – 85)
- H-FABP*: 18 µg/L (<7)

H-FABP*: Heart-type Fatty Acid Binding Protein: Raised

a. What is the most probable diagnosis?
b. Write ONE possible role of H-FABP in the diagnosis of Coronary Artery Disease?

Write your Answers here

Answers

Patient No 35

(Recent Updates)

a. Myocardial Infarction

b. It is reported to be an early marker of MI

Explanation[1]

a. There is dire need of a marker which can be helpful in diagnosis of MI in the first 2-3 h as Troponins typically peak after 10-12 h of the event.
b. H-FABP is a small protein which is released in the circulation very early in an event of myocardial ischemia.
c. So H-FABP is being evaluated as early marker of MI but results are variable.

References

1. Christopher Carroll, Mohamad Al Khalaf, John W Stevens, Joanna Leaviss, Steve Goodacre, Paul O. Heart type Fatty Acid Binding Protein as an Early Marker for Myocardial Infarction Systematic Review and MetaAnalysis N Eng Med J. 2013;30(4):280286.

Diabetes Mellitus

Patient No 36

A 60 years old male has type 2 diabetes mellitus, hypertension and stage 2 chronic kidney disease. He has reported to A&E of a hospital with abdominal pain, vomiting and confusion state. His pulse is 58/min and BP is 85/40 mmHg. He is on a long list of medication but his wife suspects he has erroneously overdosed ***metformin.*** His lab profile was:

- pH 7. 10 (7.35-7.45)
- Base Excess - 9.0 (<+3- -3)
- PCO_2 25.2 mmHg (35-45)
- PO_2 57 mmHg (80-100 mm Hg)
- Bicarbonate 11.8 mmol/L (22-28)
- Na 142 mmol/L (138-145 mmo/L)
- K 6.3 mmol/L (3.5-5 mmo/L)
- Chloride 83.0 mmol/l (95-105 mmol/l)
- Urea 34.0 mmol/l (2.5-7.7 mmol/l)
- Creatinine 760 µmol/l (50-120 µmol/l)
- Prothombin time: Prolonged

a. What is the most likely diagnosis?

b. Name ONE most important lab investigation to confirm the diagnosis

Write your Answers here

P

Answers

Patient No 36

a. Lactic Acidosis (due to overdosed Metformin and co-morbidities)

b. Plasma Lactate levels

Explanation[1]

a. Lactic acidosis is very common cause of metabolic acidosis
b. Biguinide overdosage is notorious to cause lactic acidosis
c. Phenformin has been withdrawn due to marked lactic acidosis
d. Lactic acidosis due to metformin over-dosage occurs mainly in patients with co-morbid conditions. In an otherwise normal person it is rare.
e. Please see attached article for biochemical mechanism of lactic acidosis due to metformin

References

1. Metformin overdoasage www.uptodate.com ©2015 UpToDate

Patient No 37

A 15-year-old boy, diagnosed with Type 1 diabetes mellitus 6 years ago, presented with a 36-hour history of malaise, abdominal pain, and a reduced conscious level. On examination he was drowsy and breathing rapidly and deeply. His biochemistry on admission was as follows:

- Sodium 120 mmol/L
- Potassium 5.9 mmol/L
- Bicarbonate 8.4 mmol/L
- Urea 14.9 mmol/L
- Creatinine 444 µmol/L
- Glucose 52.0 mmol/L
- Urine ketones +++

a. Which ketone species is likely to be present in the largest concentration in his serum?

b. State TWO possible causes for this episode of diabetic ketoacidosis in this patient.

Write your Answers here

Answers

Patient No 37

a. β-hydroxbutyrate
b. Missed taking insulin and Underlying infection

Explanation[1]

a. Ketoacidosis is characterized by the presence of acetoacetic acid (true ketone), beta hydroxybutyrate (derivative of acetoacetate) and acetone (a true ketone but not an acid)
b. In normal serum ratio of acetoacetic acid and beta hydroxybutyrate is 1:1
c. In DKA this ratio is disturbed in favour of beta hydroxybutyrate and in severe DKA, the ratio of beta hydroxybutyrate and acetoacetic acid may become 10:1
d. Nitropruside test (Rothra`s test) routinely carried out in urine and serum does not react with beta hydroxybutyrate
e. Colorimetric test for beta hydroxybutyrate are now available and recommended test

References

1. Diabetic Ketoacidosis. www.uptodate.com ©2015 UpToDate

Patient No 38

A 33 years old female is pregnant for 15 weeks. Her BMI is 33 Kg/m^2. Her father was also diabetic. Her biochemical tests shows:

- Fasting Plasma Glucose: 7.8 mmol/L
- HbA1c : 7.5 % (59 mmol/mol)

a. What is the most likely diagnosis?

b. Which etiological class of Diabetes Mellitus (DM) this patient belongs to?

Write your Answers here

Answers

Patient No 38

a. Overt DM (DM in Pregnancy)

b. Type 2 DM

Explanation[1,2]

Hyperglycaemia can cause dreadful complications in pregnancy. It can present with more than one faces:
a. Pre-gestational DM: This term is sometimes used for women who are known cases of DM and become pregnant. Diagnosis of these cases is not required during pregnancy
b. Overt DM:. Full blown DM ***diagnosed at any stage of pregnancy is called Overt DM***. The incidence of this category is increasing with worsening life style and increased prevalence of type 2 DM in women. WHO has endorsed this category in 2013 but with the term '***Diabetes is Pregnancy'*** (without the word 'Overt').
c. Gestational DM (GDM): Women with onset or first recognition of abnormal glucose tolerance ***during any stage of pregnancy*** (other than those in overt category).

Diagnosis of Overt DM

Overt DM is diagnosed at any stage of pregnancy if ONE of the following is present:

- Glycosylated Haemoglobin (A1c)*: ***≥6.5%***
- Fasting Plasma Glucose: ***≥7.0 mmol/L (126 mg/dl)***
- Random blood glucose**: ***≥ 11.1 mmol/l (200 mg/dl)***
- 2-h plasma glucose (following a 75g oral glucose load) : ***≥11.1 mmol/l***

** Should be carried out only in first trimester by an NGSP certified method.*

*** Should NOT be advised except in situations where suspicion of DM is strong*

Diagnosis of GDM

GDM is diagnosed at any stage of pregnancy if any one of the following is present following a 75g oral glucose load:

- Fasting : Between 5.1-6.9 mmol/l (92 -125 mg/dl)
- 1 hour: >10.0 mmol/l (180 mg/dl)
- 2-hour: Between 8.5 – 11.0 mmol/l (153-199 mg/dl)

References

1. American Diabetes Association Standards of Medical Care In Diabetes 2015
2. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy WHO/NMH/MND/13.2 (2013)

Patient No 39

A 21 years old male has been diagnosed to have Diabetes Mellitus (DM). His father, paternal uncle and grandfather were also diabetic. His BMI is 21Kg/m^2 He responded very well to sulfonylureas and did not require insulin for control. At the time of diagnosis his important lab investigations showed following results:

- Fasting Plasma Glucose: 9.2 mmol/L (166 mg/dl)
- Urine Glucose : +++
- Anti-Islet cell antibodies: Negative
- Anti-GAD antibodies: Negative.

a. Name the type of DM, he is suffering from?

b. Name the laboratory investigations required for confirmation of his diagnosis

Write your Answers here

Answers

Patient No 39

(Recent Updates)

a. Maturity Onset Diabetes of the Young (MODY)

b. Genetic Testing

Explanation[1]

a. MODY is different from type 2 DM because this is a group of monogenetic disorders.
b. It is classified in *'other specific types'* of WHO classification
c. About 6 types of MODY have been described with different genetic defects and clinical features (Please see next slide)
d. High paternal inheritance and glycosuria are characteristics of type 3 (hepatocyte nuclear factor 1 alpha defect)

References

1. Classification of diabetes mellitus and genetic diabetic syndrome www.uptodate.com ©2015

Patient No 40

A 61 years old male is a known patient of Diabetes Mellitus (DM) and is presently on insulin therapy for the control of his DM. He has reported in A&E Department of a hospital with symptoms of hypoglycemia.

His capillary blood glucose measured in hospital is *3.6 mmol/L (65 mg/dl).*

a. Which class of hypoglycemia this patient is suffering from?

b. What advise you will give to this patient regarding management of these symptoms in future?

Write your Answers here

Answers

Patient No 40

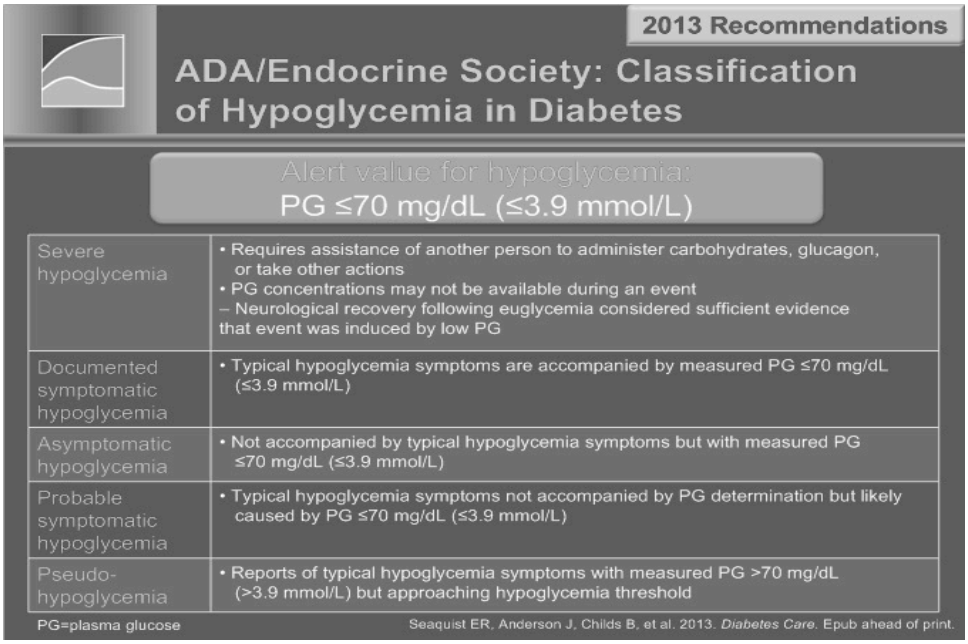
(Recent Updates)

a. Documented Symptomatic Hypoglycemia

b. The treatment plan has to be revised to avoid such incidence

Explanation[1]

a. No need to demonstrate Whipple`s triad in diabetics.
b. Ignoring such symptoms in diabetics can be dangerous.
c. Hypoglycaemia in diabetics, may be documented or undocumented, should be taken as an urgent issue
d. Some modification of treatment should be advised to avoid untoward incidence while patient is driving etc.



References

1. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of theAmerican Diabetes Association and the Endocrine Society. J Clin Endocrinol Metab 2013; 98: 1845.

Patient No 41

A 47 years old male has been diagnosed to be having type 2 diabetes mellitus. He is being investigated for the assessment of glucose control. A new marker 1, 5-Anhydroglucitol (1, 5-AG) was also analysed. The result shows:

- Fasting Plasma Glucose : 11.2 mmol/L
- HbA1c: 7.6 %
- 1,5-AG: 6 µg/ml

a. What does the result of 1, 5-Anhydroglucitol (1, 5-AG) indicates in this patient?

b. Write ONE biochemical basis of change in 1,5-AG in in this patients.

Write your Answers here

Answers

Patient No 41

(Recent Updates)

a. Uncontrolled DM

b. Glucose competes with 1, 5 AG for reabsorption in kidney. When glucose is high, 1,5 AG cannot be reabsorbed and is decreased in serum

References

1. Elizabeth Selvin, Andreea M. Rawlings, Morgan Grams, Josef Coresh,Ronald Klein, Michael Steffes. Association of 1,5-Anhydroglucitol with Diabetes and Microvascular Conditions. Clinical Chemistry 60:11:1409–1418 (2014)

Patient No 42

A 31 years old pregnant female has BMI of 32 Kg/m^2. Following are the results of her biochemical investigations carried out at 26^{th} week of pregnancy:

OGTT with 75 g glucose

- Fasting Plasma Glucose : 6.2 mmol/L
- One hour: 11.2 mmol/L
- Two hours: 9.3 mmol/L

HOMA-IR: 6.4 (<2.2)

She is subject of a study carried out to evaluate the role of Adeponectin and Insulin Like Growth Factors 1 (IGF1) in GDM. The researchers are also studying the association of High Molecular Weight (HMW) adeponectin with insulin resistance

a. What is your expectation of Adeponectin and IGF1 levels in this patient (increased or decreased)
b. What is the expected HMW Adeponectin to total adeponectin ratio in this patient (increased or decreased)

Write your Answers here

Answers

Patient No 42

(Recent Updates)

a. Decreased

b. Decreased

References

1. Adiponectin and IGFBP-1 in the development of gestational diabetes in obese mothers. BMJ Open Diabetes Research and Care 2014;2: e000010. doi:10.1136/ bmjdrc-2013-000010

Patient No 43

A 10 years old boy, who is a known patient of Type 1 Diabetes Mellitus, is admitted in an Intensive Care Unit in semi-conscious state. His biochemical picture shows:

- Plasma Glucose 15.6 mmol/L
- pH : 7.21 (7.35-7.45)
- Na : 140 mmol/L (135-150)
- K : 6.2 mmol/L (3.5-5.0)
- Cl : 100 mmol/L (98-106)
- HCO_3 : 13.8 mmol/L (22-28)
- Anion Gap: 26
- Serum Ketone (By Nitroprusside test): Negative

a. Why nitroprusside test is negative in this patient in spite of evidence of Diabetic Ketoacidosis (DKA)?

b. Name the biochemical tests which can be more useful in this patient to diagnose DKA.

Write your Answers here

Answers

Patient No 43

(Recent Updates)

a. Nitroprusside reacts with acetoacetate and acetone and not with beta hydroxybutyrate.

b. Estimation of beta hydroxybutyrate in the blood

References

1. Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis. www.uptodate.com ©2015

Patient No 44

A 15 years old male has been referred to you for the investigation of polyuria which he has developed for the last a few weeks. He is a known patient of Type 1 DM for the last 7 years. He has loss of vision due to a cranial nerve lesion diagnosed in an Ophthalmology Clinic. He also complains of hearing loss. An examination by ENT specialist reveals that he is gradually developing neural deafness. His plasma glucose and protein: Creatinine Ratio are within desirable ranges.

Water deprivation test was done with following results:

Six hours after Fluid Restriction:

- Serum Osmolality : 294 mOsmol/L
- Urine Osmolality: 128 mOsmol/L

Post Vasopressin

- Serum Osmolality : 282 mOsmol/L
- Urine Osmolality: 786 mOsmol/L

a. What is the most probable diagnosis?
(Please name one disease in which all these features fit in)

Write your Answers here

Answers

Patient No 44

Wolfram syndrome comprising type 1 diabetes mellitus and optic atrophy, known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness).

Explanation[1]

1. Rare disease (Rare disease are diagnosed by consultants!!). Constellation of features mentioned in the two case reports in the accompanying literature

References

1. Wolfram Syndrome presenting with optic atrophy and diabetes mellitus: two case reports. http://www.casesjournal.com/content/2/1/9355

Female Reproductive Endocrinology

Patient No 45

A 32 years old female has an adenexal mass for which she is undergoing surgery. Her OVA1 panel was carried out to assess the risk of malignancy (from a QUEST Lab USA). The result was:

- OVA1 Score: 6.2

a. What is the probability of presence of malignancy in this woman (Low or high)

b. Name FIVE biochemical tumour markers which are included in OVA1 panel.

Write your Answers here

Answers

Patient No 45

a. High

b. Two are up regulated (CA 125 II, beta 2 microglobulin) and three down regulated (transferrin, transthyretin, apolipoprotein A1

Explanation[1]

Panels of Ovarian Tumour Markers

a. OVA-1 : Includes Five Tumour markers (previous slide)
b. The Risk of Malignancy Algorithm (ROMA) includes CA 125 and HE4 (>150pmol/l)
c. Risk of malignancy index (RMI) combines serum CA 125, pelvic ultrasound, and menopausal status into an index score to predict the risk of ovarian cancer in women with an adnexal mass. It is primarily used in the UK.

References

1. Serum biomarkers for evaluation of an adnexal mass for epithelial carcinoma of the ovary, fallopian tube, or peritoneum. www.UpToDate.com 2015

Patient No 46

A 46 years old female is a known patient of ovarian fibroma. She presented with abdominal distension and dyspnoea for the last one week. Clinical Examination of the abdomen shows presence of free-flowing fluid in the peritoneal cavity. X-Ray chest shows bilateral pleural effusion. Her ascitic and pleural fluids were aspirated. Some of biochemical findings were:

- Serum Albumin: 38 g /L
- Ascitic Fluid Albumin: 12 g/L
- Pleural Fluid Albumin: 10 g/L
- Serum LD: 384 U/L
- Pleural Fluid LD: 149 U/L

a. What is the most probable diagnosis?

b. Classify ascites and pleural effusion on the basis of these findings.

Write your Answers here

Answers

Patient No 46

a. Meigs Syndrome

b. High-grade ascites and transudative pleural effusion

. Explanation[1]

Meig Syndrome

a. A triad of benign ovarian tumor with ascites and pleural effusion that resolves after resection of the tumor is called Meigs Syndrome.
b. Ovarian fibromas constitute the majority of the benign tumors seen in Meigs syndrome.
c. It is a diagnosis of exclusion only after ovarian carcinoma is ruled out.
d. Irritation of the peritoneal surface, direct pressure on surrounding lymphatics or vessels, hormonal stimulation, and tumor torsion are some of the speculative mechanisms proposed to cause accumulation of fluid.

References

1. Meigs Syndrome: Background, Pathophysiology, Epidemiology. Medscape Reference © 2011 WebMD, LLC

Patient No 47

A 42 years old female has been referred to you by a Fertility Clinic for assessment of ovarian reserve before planning an ICSI procedure. The results of her hormonal tests were as following:

Day 3 of Regular Menstrual Cycle:

FSH : 8 mIU/ml

Oestradiol: 67 pg/ml

Clomiphene Citrate Challenge Test

Day 3 FSH: 9.6 mIU/ml

Day 10 FSH: 10.9 mIU/ml

Day 3 Oestradiol: 71 pg/ml

a. What is your opinion about the ovarian reserves in this patient?
b. Name one lab test that will be helpful in confirmation of the diagnosis.

Write your Answers here

Answers

Patient No 47

a. Good ovarian reserve

b. Anti mullarian Hormone (AMH).

Explanation[1]

Assessment of Ovarian Reserve

a. Chemical Pathologist may be required to carry out investigations related to ovarian reserve.
b. These patients are referred from Fertility Clinics for selection of patients for procedure like ICSI.
c. The tests done are :
    a. Day 3 FSH (should be <10 mIU/ml) and oestradiol (< 80 pg/ml)
        i. Similar values after Clomiphene Citrate Challenge Test
d. AMH is an excellent marker of ovarian reserve.
e. AMH >1.0 ng/mL but <3.5 ng/mL suggests a good response to stimulation

Points For Further Discussion

A lower value of FSH indicates good ovarian reserve but why Oestradiol should also be < 80 pg/ml (not > 80 pg/ml).

Answers: It is the optimum value indicating normal ovarian reserve.

References

1. Evaluation of female infertility. WWW.UpToDate.com 2015

Gastrointestinal Disorders

Patient No 48

A 7 years old male child presented with history of diarrhea, anorexia, abdominal distension and vomiting for the last 3 years. His height and weight are at 5th and 7th percentile, respectively. His Lab investigations revealed

- Blood Hb: 8 g/dl
- ALT: 40 U/L
- Urea: 4.2 mmol/L

a. What is the most likely diagnosis?

b. Suggest one most important biochemical investigation for confirmation of the diagnosis.

Write your Answers here

Answers

Patient No 48

a. Coeliac Disease

b. Xylose Absorption Test

Explanation[1]

Celiac Disease

The classic description of celiac disease, or gluten-sensitive enteropathy, includes the following three features:

a. Symptoms of malabsorption such as steatorrhea, weight loss, or other signs of nutrient or vitamin deficiency.
b. The presence of characteristic histologic changes (including villous atrophy) on small intestinal biopsy.
c. Resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months.

Pathogenesis:

d. Genetic factors
e. Autoimmunity: Celiac disease is associated with a number of autoimmune disorders including type 1 diabetes mellitus and autoimmune thyroid disease. ***tissue transglutaminase*** are highly sensitive and specific
f. A Chemical Pathologist encounters such children mostly in the Endocrine Clinic referred for growth hormone (GH) evaluation in a short stature child.
g. It is important to rule out this disease clinically and/or anti-body testing before GH testing.
h. Intestinal biopsy and anti-tissue transglutaminase antibodies are characteristic lab tests
i. In celiac disease Xylose Absorption Test is positive because of the absorptive defect

References

1. Clinical features and diagnosis of malabsorption. WWW.UpToDate.com 2015

Patient No 49

A 38 years old male complains of diarrhoea with large volume stools lasting during day and night. His biochemical profile revealed:

- Stool sodium : 125 mmol/L
- Stool potassium: 7.5 mmol/L
- Stool Osmolality Gap: 27.5 mOsm/Kg

a. Which type of diarrhoeas this patient is suffering from (Secretory or Osmotic)
b. Write the formula to calculate the osmotic gap used in this patient.

.

Write your Answers here

Answers

Patient No 49

a. Secretary diarrohea

b. Stool Osmolality Gap = 290 2 ({Na+} + {K+})

Explanation[1]

Categorization of Diarrhoea

a. Fatty diarrhoea
b. Inflammatory diarrhoea
c. Watery diarrhoea
    i. Secretory
    ii. Osmotic

Differentiation of Secretory and osmotic Diarrhoea

a. Secretory and osmotic can be differentiated by stool osmotic gap
b. Please note for calculation of stool osmolality gap a single value (290) is used.
c. Causes of secretory diarrhoea include GI tumours like carcinoid and VIPoma
d. Causes of osmotic diarrhoea include lactose and fructose intolerance
e. Breath test is used to differentiate lactose from fructose intolerance

References

a. Approach to the adult with chronic diarrhoea in developed countries www.UpToDate.com 2015

Patient No 50

A 31 years old male presented with diarhhoea, abdominal pain and heartburns. His laboratory findings are as following:

- Haemoglobin: 10.4 g/dL
- Serum Gastrin: 1121 pg/mL
- Gastric pH: 3.1

a. What is the most probable diagnosis

b. Name the dynamic (stimulation) test you will like to perform to confirm it

Write your Answers here

Answers

Patient No 50

a. Zollinger Ellison Syndrom

b. Secretin Stimulation Test

Explanation[1]

Zollinger Ellison Syndrome

a. ZES comprises gastrinomas with some clinical manifestations e.g. severe acid peptic disease and diarrhoea.
b. Serum gastrin levels > 1000 pg/ml is diagnostic of the disease but gastric pH < 4 is essential for the diagnosis of ZES.
c. If gastric pH > 4 then gastrin level may be as high as 1000 pg/ml in conditions like achlorhydria or PPI treatment
d. Secretin stimulation test is carried out for confirmation of ZES

References

1. Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis

www.UpToDate.com

Patient No 51

A 70 years old man presented in an Accident and Emergency department with symptoms of hot, red flushing of the face; severe diarrhea and asthamatic attacks:

Na	141 mmol/L	(138-145)
K	4.4 mmol/L	(3.5 - 5.0)
Chloride	110 mmol/L	(95-105)
Bicarbonate	21 mmol/L	(23_33)
Urine 5-hydroxyindoleacetic acid (5-HIAA)	:25 mg/g of creatinine	(<16)

a. What is the most likely diagnosis?

b. Name a test used to confirm this diagnosis in borderline cases?

Write your Answers here

Answers

Patient No 51

a. Carcinoid syndrome

b. Chromogranins and /or Platelet Serotonin Level

Explanation[1]

Carcinoid Syndrome

a. Carcinoid syndrome is constellation of chronic flushing and diarrhoea
b. Caused by serotonin released form metastatic tumours of the mid-gut (i.e. distal small intestine and proximal colon)
c. 5 Hydroxyindole acetic acid (5HIAA) is the principal metabolite detected in 24 h urine.
d. Other markers include serotonin and chromogranins

References

1. Diagnosis of the carcinoid syndrome and tumour localization. ww.UpToDate.com

Growth Disorders

Patient No 52

A 31 years old female presents with enlargement of the jaw, hands, and feet, which result in increasing shoe and glove size and the need to enlarge finger rings. Her biochemical tests shows:

- Urea: 6.1 mmol/l (3.5-6.7 mmol/l)
- Creatinine: 93 µmol/l (50-105 µmol/l)
- Fasting Plasma Glucose: 16.4 mmol/L (<5.6 mmol/L)

a. What is the most likely biochemical diagnosis?

b. Name ONE laboratory investigation which can be most helpful in this patient

Write your Answers here

Answers

Patient No 52

a. Acromegaly

b. IGF-1 (Glucose suppression test is contraindicated)

Explanation[1]

Acromegaly

a. Clinical features of acromegaly are quite typical and are unmistakable.
b. In patients with active acromegaly, the most important first test is IGF-1
c. If IGF-1 is normal, no further test is required.
d. If IGF-1 is raised or equivocal, Glucose Suppression Test is carried out for confirmation.
e. In scenario, patient has severe hyperglycemia and glucose suppression test is contraindicated unless glucose level is decreased

References

1. Diagnosis of Acromegaly. WWW.UpToDate.com

Patient No 53

A 32 months old boy is being investigated for short stature. He was born prematurely at about 30th weeks' gestation. At birth, he was very small (1.7 kg) and measured 14 inches in length. His growth is fully formed and proportional except some microcephaly. On examination he was found to be < 1st percentile in height and weight. All his routine biochemical, endocrine and immunological tests were normal.

He underwent growth studies which revealed:

- IgF1: Normal for age and sex
- IgFBP3: Normal for age and sex
- Growth Hormone (Basal): 4 ng/ml
- Growth Hormone (after Insulin Stimulation Test): Normal response

a. What is the most probable diagnosis in this patient?

b. Is the 'Growth Velocity' low in such patients?

Write your Answers here

Answers

Patient No 53

a. Primordial Dwarfism

b. Yes. There is growth failure

Explanation[1]

Primordial Dwarfism

a. Several poorly defined syndromes are grouped together in "Primordial Dwarfism". Seckle Syndrome is the prototype

Common features:

b. Intra-uterine Growth Retardation or Small for Gestational Age is hallmark
c. Severe growth failure persists in post-natal life
d. Height percentile is very low (<3rd percentile)
e. Their growth is generally proportional except microcephaly present in many cases
f. Growth Hormone studies are normal
g. There may be anaemia or pancytopaenia

References

1. Primordial Dwarfism. www.primordialdwarfism.com/medmain3.htm

Patient No 54

Two children with thalassemia major presented in a Growth Clinic:

1. A 7 years boy with height < 3rd percentile. Lab Tests showed:
    - IGF-1: 15.2 Ug/L (136-385)
    - IGFBP-3: 198 pg/ml (4567 – 8965)
    - Growth Hormone (GH) Stimulation Tests: Normal Response
2. A 13 years girl with height < 3rd percentile. Lab Tests showed:
    - IGF-1: 25.2 (Ug/L (136-385)
    - IGFBP-3: 198 pg/ml (4567 – 8965)
    - GH Stimulation Tests: sub-normal Response

a. What are the causes of short stature in these two thalassemic children?

b. Name TWO hormones you will like to test in the girl.

Write your Answers here

Answers

Patient No 54

a. GH insensitivity due to IGF defect and GH def due to pituitary defect

b. FSH and LH

Explanation[1]

Short Statured Thalassemic Children

a. IGF-1 axis is affected earlier due to iron deposition
b. So GH insensitivity may be present in these children
c. Later in life iron deposition also starts in pituitary and other endocrine organs causing decrease GH secretion and puberty failure
d. Absence of sex steroid also causes short stature
e. Other factors include malnutrition and Vitamin D deficiency

References

1. Thalassemia and Aberrations of Growth and Puberty. http://www.mjhid.org/article/view/4612

Inherited Metabolic Disorders

Patient No 55

A 36 years old male presented with joint pain in both knees and ankles. He also had bluish coloration of his ears and a bluish coloration of the sclera of left eye. On questioning by an astute physician he revealed that his urine turns dark blue after some interval in the bowl.

Lab investigations revealed:

- Plasma Amino acids by HPLC: All amino acids including tyrosine are within reference interval.
-

a. What is the most probable diagnosis?
b. Name the urine test that can be used for confirmation of the disease

Write your Answers here

Answers

Patient No 55

a. Alkaptonuria

b. Homogentisic acid

Explanation[1]

Alkaptonuria

a. Alkaptonuria (AKU, MIM# 203500) results from deficiency of homogentisic acid dioxygenase the third enzyme in tyrosine degradation
b. It is an autosomal recessive disorder
c. Homogentisic acid (HGA) polymerizes in a pigment which deposits in various tissues of the body (ochronosis)
d. Disease appears in 3rd to 4th decade of life
e. Diagnosis is confirmed by quantitative analysis of HGA in urine
f. Tyrosine levels are normal

References

1. Disorders of tyrosine metabolism. www.UpToDate.com

Patient No 56

A 20 days newborn presented with lethargy, poor feeding and seizures few hours after his birth. Child was brought to pediatrician who advised different lab tests. His laboratory investigations revealed:

- Fasting plasma Glucose: 2.2 mmol/L
- Plasma Lactate: 1.5 mmol/L (< 2.0)
- Serum ALT: 65 U/L
- Fasting Insulin: >36 pmol/L (< 20)
- C peptide: > 0.6 ng/ml (< 0.3)
- Urine for glucose: Negative
- Urine for ketone bodies Negative

a. What is most likely diagnosis?

b. Name one biochemical test which may be helpful in the diagnosis

Write your Answers here

Answers

Patient No 56

a. Persistent Hyperinsulinaemic Hypoglycaemia of Infants

b. Inappropriate glycemic response to glucagon at the time of hypoglycemia.

Explanation[1]

Persistent Hyperinsulinemic Hypoglycemia of Infants (PHHI)

a. Most common cause of persistent hypoglycemia of the neonates
b. It's a genetic dysregulation of insulin secretion with sporadic or familial presentation
c. Biochemical Features:
    (1) Blood Glucose < 2.2 mmol/L in response to short fasting
    (2) Inappropriately high or normal insulin in the face of hypoglycemia
    (3) Low FFA and ketone in spite of hypoglycemia
    (4) Inappropriate glycemic response to glucagon i.e. increase of glucose by 1.7mmol/L indicates retention of hepatic glycogen and hyperinsulinemia

References

1. Pathogenesis, clinical features, and diagnosis of Persistent Hyperinsulinaemic Hypoglycemia of infancy. www.uptodate.com ©2015

Patient No 57

An infant presents with progressive neurological impairment with mental retardation (IQ not improving with age). He also has mousy odor, skin pigmentation and abnormal physical growth. His biochemical findings are:

- Acidosis: Negative
- Ketones : +
- Ammonia (NH3): Normal
- Lactate: Normal
- Glucose: Normal
- Calcium: Normal

Plasma Amino Acid Analysis by HPLC *: Phenylalanine Markedly Raised*

a. What is the most probable diagnosis?
b. Name ONE biochemical test which can be used for screening and diagnosis of this disease

Write your Answers here

Answers

Patient No 57

a. Phenylketoneuria

b. Serum Phenylalanine Level

Explanation[1]

Phenylketonuria

- PKU is an important part of Newborn Screening part in many countries
- PKU (MIM#261600) is a disorder with accumulation of amino acid phenylalanine.
- It results from a deficiency of phenylalanine hydroxylase (PAH)
- If untreated is characterized by intellectual disability (mental retardation).
- Tyrosine concentration is normal or low normal.

References

1. Overview of phenylketonuria. WWW.UpToDate.com 2015

Patient No 58

A 9 hours of age newborn is reported to have poor feeding and hypothermia.

- Plasma glucose: 1.4 mmol/L

His plasma glucose came within reference range (for the age) at 3rd day and the baby was discharged fit.

a. What is the most probable diagnosis?

b. Write THREE likely causes of this condition.

Write your Answers here

Answers

Patient No 58

a. Transient Hypoglycemia of Newborn

b. Causes:

1. Prematurity, intrauterine growth retardation
2. Asphyxia, hypothermia
3. Sepsis
4. Infant of diabetic mother
5. Erythroblastosis fetalis

Explanation[1]

References

1. Update on Investigating hypoglycemia in childhood. Ann Clin Biochem 2011: 1–12. DOI: 10.1258/acb.2011.011012

Patient No 59

An infant has been brought to a Pediatrician with history of poor feeding, lethargy and rapid breathing. There is also history of poor muscle tone, seizures abnormal eye movements and poor visual tracking. He has severe neurological deterioration and brain malformations has been demonstrated on neuroimaging. His biochemical findings are:

- Acidosis: +++
- Ketones : +
- NH_3: +
- Lactate: +++
- CSF Lactate: ++++
- Glucose: Normal
- Calcium: Normal
- Gutherie`s Test Negative

a. What is the most probable diagnosis?

b. What special precautions in diet should be taken while managing this case?

Write your Answers here

Answers

Patient No 59

c. Pyruvate Dehydrogenase Complex Deficiency (Congenital Lactic Acidosis also taken as correct Answers)

d. Ketogenic diets, with high fat and low carbohydrate

Explanation[1]

Congenital Lactic Acidosis

a. Congenital Lactic Acidosis is the broad category of Inborn Errors of Metabolism
b. Inherited mitochondrial diseases are the commonest causes of congenital lactic acidosis i.e. ***Pyruvate Dehydrogenase Complex Deficiency*** and ***Pyruvate Carboxylase Deficiency***
c. Other Causes:
    a. Biotin deficiency
    b. Glycogen storage disease
    c. Sepsis etc.

Point For Further Discussion

How to differentiate between ***Pyruvate Dehydrogenase Complex Deficienc***y and ***Pyruvate Carboxylase Deficiency*** based simple biochemical tests like lactate and pyruvate.

Answers: By Carrying out Pyruvate: Lactate Ratio

References

1. NORD. http://rarediseases.org/rare-diseases/congenital-lactic-acidosis/

Patient No 60

A 3 days old newborn presented with refusal to feed, hypotonia, failure to thrive and seizures. His laboratory investigations revealed:

- pH: 7.32 (7.35 - 7.45)
- PCO_2: 33 mmHg (35 – 45)
- HCO_3 : 18.2 mmol/L (20 – 28)
- Plasma glucose (R) 2.2 mmol/L (>2.0)
- Serum potassium : 4.2 mmol/L (3.6–5.2)
- Serum Sodium: 139 mmol/L (132-145)
- Urine Ketones: Negative
- Plasma Aminoacids (By HPLC): Glycine 938 µmol/L (<330)
- CSF Aminoacids (By HPLC): Glycine 813 µmol/L (<7.5)

a. What is the most probable diagnosis?

b. Name ONE important differential diagnosis.

Write your Answers here

Answers

Patient No 60

a. Non-ketotic Hyperglycinemeia

b. Organic Acidemias

Explanation[1]

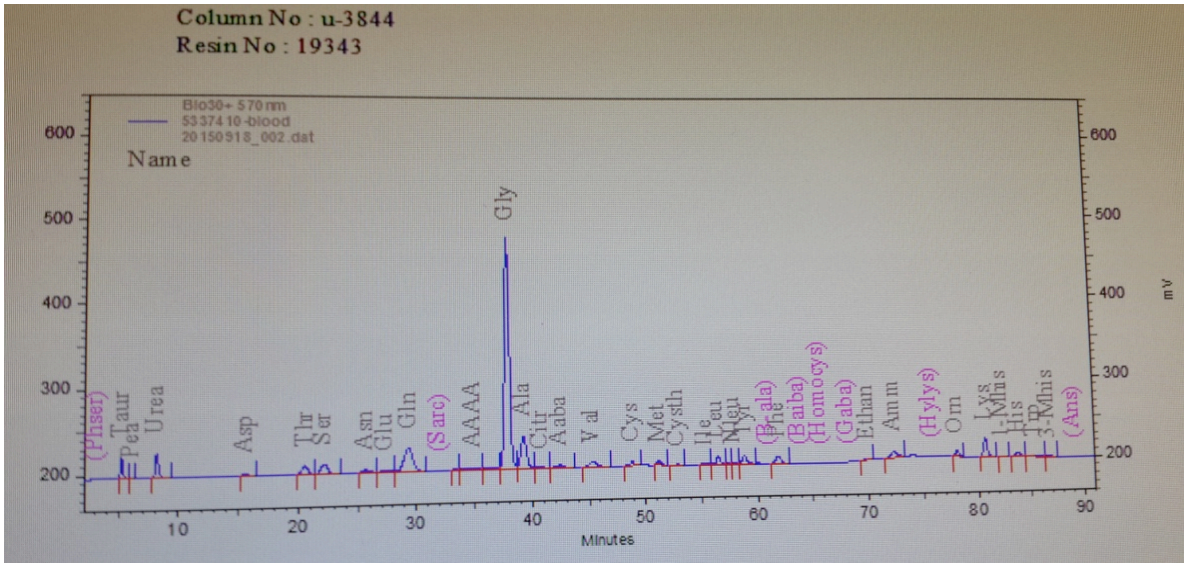
a. First remember it is not 'Hyperglycaemia'!

b. It is due to defective metabolism of amino acid Glycine which accumulates in toxic concentrations

c. High CSF and serum glycine is the hallmark of the disorders

At AFIP Rwp this was the first case diagnosed on newly installed HPLC (biochrome) system for Amino Acid analysis

"Glycine Peak" on HPLC



References

1. Non-Ketotic Hyperglycinaemia: NORD. www. National Organization for Rare Diseases.com

Patient No 61

A 3 days old baby girl presented with lethargy, anorexia, hypoventilation, hypothermia and seizures. and coma. Her biochemical investigations revealed

- pH: 7.48 (7.35 - 7.45)
- PCO_2: 44 mmHg (35 – 45)
- HCO_3 : 32 mmol/L (20 – 28)
- Plasma glucose (R) 5.9 mmol/L (5.6-6.9)
- Serum potassium : 4.4 mmol/L (3.6–5.2)
- Plasma Ammonia: 874 mmol/L (<35)
- Plasma Amino Acid Analysis reveals:
    - Citrulin: Decreased
    - Ornithine: Decreased
    - Glutamine Increased

a. What is most probable group of Metabolic Disorders present in this baby?

b. Name a urine test which can be helpful in finding the exact biochemical defect.

Write your Answers here

Answers

Patient No 61

a. Urea Cycle Defect

b. Urine Orotic Acid

Explanation[1]

Urea Cycle Defects

a. Disease usually present during first a few days of life
b. Usual symptoms include somnolence, inability to maintain normal body temperature, and poor feeding, followed by vomiting, lethargy, and coma.
c. Very high Plasma Ammonia (>100 mmol/L) is an important finding
d. Absence of Metabolic Acidosis distinguishes it from other inherited metabolic disorders. Metabolic Alkalosis (not in all cases) may be present.
e. Amino acid pattern in plasma helps in diagnosis of various enzyme deficiencies. Following is an example
f. Decreased Citrulin, Decreased ornithine and increased Glutamine may be due to deficiency of either carbamyl phosphate synthetase (CPS) or ormithine transcarbamylase (OTC).
g. Urine Oratic acid level can differentiate the two conditions (Please see the PDF document *"Diagnostic algorithm for initial evaluation of hyperammonemia"*

References

1. Evaluation of female infertility. WWW.UpToDate.com 2015

Patient No 62

An infant has been brought in a Paediatric Clinic with history of attacks of hypoglycemic featured by lethargy, nausea, and vomiting which rapidly progresses to coma within 1–2 h. Seizures also occur. His biochemical findings during the attacks are usually like following:

- Hypoglycaemia precipitated by fasting
- Acidosis: +
- Ketone bodies: Inappropriately Low
- Lactate: +
- Fasting Insulin: Normal
- Postprandial total acylcarnitine levels: <25-50% of normal

What is the most probable diagnosis?

Write your Answers here

Answer

Patient No 62

Fatty acid oxidation disorder

Explanation[1]

Fatty acid oxidation (FAO) disorders usually present in early infancy as acute life-threatening episodes of hypoketotic, hypoglycemic coma induced by fasting or febrile illness. These include carnitine deficiency, fatty acid transportation defects, and defects of beta-oxidation enzymes.

Classification:

1. Carnitine cycle defects
2. ß-Oxidation Defects
    - Very-long-chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency
    - Medium-chain Acyl-CoA Dehydrogenase (MCAD) Deficiency
    - Short-chain Acyl-CoA Dehydrogenase (SCAD) Deficiency.
3. Electron Transfer Defects
4. Ketogenesis defects

References

1. Wanders RJA, Vreken P, den Boer ME et al (1999) Disorders of mito- chondrial fatty acyl-CoA - oxidation. J Inherit Metab Dis 22:442- 487

Patient No 63

An 8 months old baby is admitted in a hospital as he is failing to thrive.

Urine Amino Acids By HPLC Analysis shows:

Urine Homocystine/Creat ratio:	9	µmol/mmol (0 - 5)

Urine Organic Acids By GC/MS shows:

Urine Ketones:		Negative by Multistix
Urine *MMA/Creatinine ratio:	1413	µmol/mmol (0 - 30)
Urine Methylcitrate/Creat ratio:	50	µmol/mmol (0 - 25)
Urine Creatinine :		1.3 mmol/L

*MMA: Methyl Malonic Acid

What is the most probable diagnosis?

Write your Answers here

Answer

Patient No 63

Organic Aciduria (Methyl Malonic Aciduria)

Explanation[1]:

a. Organic acidemias, characterized by increased excretion of organic acids in urine, result primarily from deficiencies of specific enzymes in the breakdown pathways of amino acids or from enzyme deficiencies in beta oxidation of fatty acids or carbohydrate metabolism. Organic acids also are found in the urine of some patients with mitochondrial disease

b. They are characterized by their specific urinary organic acid profiles using GC-MS or abnormal acylcarnitines on tandem MS e.g. In Propionic Acidemia there is increased concentrations of free propionic acid in blood and urine, multiple organic acid byproducts(propionylcarnitine,3-hydroxypropionate, and methylcitrate) appear in urine

Patient No 64

A 14 month child has repeated upper airway obstruction and frequent ear, nose and throat infections. She has short stature, hepatosplenomegaly, increasing facial dysmorphism, cardiac disease, progressive learning difficulties and corneal clouding. Her biochemical findings are :

- Urine heparan sulfate : Increased
- Urine keratan sulphate: Increased

What is the most probable diagnosis?

Write your Answers here

Answers

Patient No 64

Mucopolysaccharidosis

Patient No 65

A 10 months child presents with protruded abdomen, truncal obesity, short stature, hepatomegaly, and growth delay. His biochemical findings are :

- Attack of hypoglycaemia on brief fast
- Ketones : +
- NH3: Normal
- Lactate: +++
- Triglycerides: Increased
- Insulin: Normal

What is the most probable diagnosis?

Write your Answers here

Answers

Patient No 65

Glycogen Storage Disease Type I

Lipid Disorders

Patient No 66

A 39 years old male is known to have high cholesterol and triglycerides at multiple occasions in the past. His two brothers have also similar pattern of lipid abnormality. His BMI is 28 Kg/m^2. He is not hypertensive. His recent biochemical profile indicates:

- Fasting Plasma Glucose: 4.4 mmol/L (79 mg/dl)
- Cholesterol : 9.4 mmol/L (362 mg/dl)
- Triglycerides : 7.2 mmol/L (634 mg/dl)
- LDL Chol (measured): 4.3 mmol/L (164 mg/dl)
- HDL Chol (measured): 0.95 mmo/L (37 mg/dl)

a. Give TWO most important differential diagnosis

b. Name ONE laboratory test which can be very helpful in differentiating these two conditions.

Write your Answers here

Answers

Patient No 66

a. Familial Combined Hyperlipidaemia and Metabolic Syndrome

b. Apolipoprotein B

Explanation[1]

Familial Combined Hyperlipidaemia (FCHL)

a. FCHL is characterized by hypercholesterolemia and/or hypertriglyceridemia in at least two members of the same family with intra-individual and intra-familial variability.
b. It is an important predisposing factor for premature CHD
c. FCHL is one of the most common genetic hyperlipidemias in the general population

Difference between Metabolic Syndrome (MS) and FCHL

d. Apo B is the main differentiating marker, it is high in FCHL, but not in MS.
e. LDL-C is usually normal or rather low in MS as compared to FCHL
f. The lipid phenotype is more variable in FCH than in MS (both in individuals and families)
g. The inheritance of the disorder is much more evident in FCH, and life style is much less relevant on FCH clinical manifestation and prognosis than on MS
h. Earlier clinical and laboratory manifestation in FCH

References

1. Practical guidelines for familial combined hyperlipidaemia diagnosis: an up-date

Vascular Health and Risk Management 2007:3(6) 877–886

Patient No 67

A 3 months old male infant is somewhat restless probably due to abdominal pain. He has a papular rash and enlarged liver and readily palpable spleen. There is no evidence of jaundice and the child appears well.

His lipid profile revealed:

- Serum appearance: 'raspberry milkshake'
- Overnight standing test at 4^{0} C: Creamy ring at the top
- Cholesterol : 3.4 mmol/L (131 mg/dl)
- Triglycerides : 25.2 mmol/L (2217 mg/dl)
- LDL Chol (measured): 2.34 mmol/L (190 mg/dl)
- HDL Chol (measured): 1.12 mmo/L (43 mg/dl)

a. Which type of hyperlipidemia is present in this patient according to Fredrickson classification of hyperlipidemias?
b. Name ONE enzyme which may be deficient in this patient

Write your Answers here

Answers

Patient No 67

a. Type 1

b. Lipoprotein Lipase

Explanation[1]

Lipoprotein Lipase Deficiency

a. Type1 Hyperlipoproteinaemia
b. Characterized by very high triglycerides and normal cholesterol
c. In a Routine Chem Path lab can be diagnosed by overnight tube test i.e. putting the serum sample of the patient at 4^0 C.
d. A ring at the top of the tube indicates increased chylomicrons in the sample
e. Usually present in children < 1 y of age
f. Abdominal pain may be due to pancreatitis
g. Hepato-splenomegaly may also be present.

References

1. Climb National Information Centre for Metabolic Diseases

Patient No 68

A 3 months old male infant is somewhat restless probably due to abdominal pain. He has a papular rash and enlarged liver and readily palpable spleen. There is no evidence of jaundice and the child appears well.

His lipid profile revealed:

- Serum appearance: 'raspberry milkshake'
- Overnight standing test at 4^{0} C: Creamy ring at the top
- Cholesterol : 3.4 mmol/L (131 mg/dl)
- Triglycerides : 25.2 mmol/L (2217 mg/dl)
- LDL Chol (measured): 2.34 mmol/L (190 mg/dl)
- HDL Chol (measured): 1.12 mmo/L (43 mg/dl)

c. Which type of hyperlipidemia is present in this patient according to Fredrickson classification of hyperlipidemias?

d. Name ONE enzyme which may be deficient in this patient

Write your Answers here

Answers

Patient No 68

c. Type 1

d. Lipoprotein Lipase

Explanation[1]

Lipoprotein Lipase Deficiency

h. Type1 Hyperlipoproteinaemia
i. Characterized by very high triglycerides and normal cholesterol
j. In a Routine Chem Path lab can be diagnosed by overnight tube test i.e. putting the serum sample of the patient at 4^0 C.
k. A ring at the top of the tube indicates increased chylomicrons in the sample
l. Usually present in children < 1 y of age
m. Abdominal pain may be due to pancreatitis
n. Hepato-splenomegaly may also be present.

References

1. John D Brunzell. Familial Lipoprotein Lipase Deficiency GeneReviews® [Internet] 2014. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1308

Patient No 69

A 1 month old infant has a highly chylous sample. Her lipid profile is as following:

- Cholesterol : 3.4 mmol/L
- Triglycerides : 22.1 mmol/L
- LDL Chol (measured): 1.34 mmol/L
- HDL Chol (measured): 1.1 mmo/L
- Overnight incubation of serum sample at 4^0C shows a ring on the top of a clear sample

a. What is the most probable diagnosis?

b. Which type of hyperlipidemia this infant is suffering from as per Frederickson Classification.

Write your Answers here

Answers

Patient No 69

a. Lipoprotein Lipase Deficiency

b. Type I Hyperlipidaemia

Explanation[1]

Lipoprotein Lipase Deficiency

a. A childhood hyperlipidemia
b. Severe hypertriglyceridemia is the characteristic finding
c. It's a type I hyperlipidemia mainly due to hyperchylomicronemia
d. Abdominal pain or pancreatitis may be the presenting feature.

References

1. John D Brunzell. Familial Lipoprotein Lipase Deficiency GeneReviews® [Internet] 2014. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1308

Patient No 70

(Recent Updates)

A 57 years old male is a known patient of Ischemic Heart Disease for which he underwent CABG about 5 years ago. He and many of his closed relatives had hypercholesterolemia for which he is being given statins at the maximum does. Unfortunately his tolerance to this medicine is very poor and he experiences a lot of muscular pains. His recent biochemical profile shows:

- Total Cholesterol: 6.5 mmol/L
- Triglycerides: 0.78 mmol/L
- LDL-C: 4.7 mmol/L
- HDL-C: 1.1 mmol/L
- ALT: 123 U/L
- CK: 327 U/L

a. What is most likely diagnosis?

b. Name ONE very recently reported ***drug*** which can be helpful to this patient (Please write full biochemical name)

Write your Answers here

Answers

Patient No 70

a. Familial Hypercholesterolaemia (FH)

b. Evolocumab (PCSK9 Inhibitor)

Explanation[1]

Salient Features of FH

a. Inheritable, autosomal dominant disorder
b. Usually due to mutations in LDL receptor gene that result in decreased clearance of LDL particles from plasma
    a. Other mutations include those in the Apo B and PCSK9 genes
c. Clinical manifestations include
    a. Severe hypercholesterolemia due to accumulation of plasma LDL
    b. May be accompanied by cholesterol deposition in tendons and skin (xanthomas) and in the eyes
    c. Evidence of CVD early in life

The Phenotype of FH May Reflect LDL-R, Apo B, or PCSK9 Mutations

a. LDLR codes for the LDL Receptor, which clears LDL particles from the circulation by binding to surface Apo B
b. PCSK9 induces degradation of LDLR
c. FH may be caused by mutations in Apo B, LDL-R, or PCSK9

Points For Further Discussion

Normal function of PCSK9 is degradation of LDL Receptors (LDLR). So its action leads to increased LDL-C as occurs in other forms of FH. Why mutation in the gene forming PCSK9 leads to increased LDL-C?

Answers: It is a gain of function mutation which leads to degration of the LDL Receptors and FH.

d. Can there be Hypocholesterolaemia in a patient with PCSK9 mutation?

Answers: Yes. If the mutation is loss of function

e. Name ONE feature which differentiates FH from Familial Combined Hyperlipidaemia.
Answers: Presence of Xanthomas

References

1. Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med 2015;372:1500-9.

Patient No 71

A 19 year old male has strong family history of dyslipidaemia and Coronary Artery Disease. His biochemical investigations revealed:

- Cholesterol : 5.4 mmol/L (208 mg/dl)
- Triglycerides : 3.1 mmol/L (279 mg/dl)
- LDL Chol (measured): 2.14 mmol/L (83 mg/dl)
- HDL Chol (measured): 1.01 mmo/L (39 mg/dl)
- Apolipoprotein B: 3.1 g/L (0.7 – 1.74)
- LDL-C / Apo B ratio: 0.69 (>1.4)

a. Give TWO most important differential diagnosis
b. Name the most probable sub-type of LDL particles present in this patient in greater excess.

Write your Answers here

Answers

Patient No 71

(Recent Updates)

a. Familial Combined Hyperlipidemia and Hyperapobetalipoproteinemia

b. Small dense LDL

Explanation[1]

Familial Combined Hyperlipidaemia (FCHL)

a. Metabolic disorder characterized by
b. Increased in triglycerides and / or cholesterol levels in at least two members of the same family
c. Intra-individual or intra-familial variability of lipid phenotype
d. Increased risk of premature coronary heart disease
e. Overproduction of hepatically derived Apolipprotein B100 associated with VLDL.
f. LDL phenotype B (small, dense LDL particles) make it very strongly atherogenic
g. Raised LDL-C levels and Triglyceride levels
h. Reduced HDL -C
i. LDL-C / Apo B ratio < 1.2 (Normal > 1.4)

Variants of FCHL

a. *Hyperapobetalipoproteinemia*
    i. Characterized by over production of Apo-B
    ii. Normal concentration of LDL-C
    iii. LDL-C/Apo-B ratio < 1.2 (normal >1.4)
b. *Lipoprotein Lipase (LPL) deficiency*
    i. Characterized by increased triglycerides
    ii. Confirmed by measuring LPL activity

References

1. Inherited disorders of LDLcholesterol metabolism. www.uptodate.com ©2015

Patient No 72

A 51 years old male has recently returned from United States. He is a known patient of Coronary Heart disease. He has shown you his recent Lipid tests from a state-of-the-art US lab to seek your opinion:

- Cholesterol: 274 mg/dl
- Triglycerides: 215 mg/dl
- LDL-C: 165 mg/dl
- HDL-C: 37 mg/dl
- Non-HDL-C: 237 mg/dl
- Lipoprotein – Associated Phospholipase A2 (Lp-PLA2) Activity: 576 nmol/min/m (< 284)

a. What raised Lp-PLA2 indicates in this patient?

b. To which Lipoprotein this enzyme (Lp-PLA2) is bound to in circulation?

Write your Answers here

Answers

Patient No 72

(Recent Updates)

a. Lp-PLA2 is a marker of atherosclerosis

b. Mostly LDL but also to HDL

Explanation[1]

Lipoprotein – Associated Phospholipase A2 (Lp-PLA2)

a. This marker is now available in the labs of developed countries as a part of the risk assessment of Coronary Artery Disease
b. It is implicated in many events leading to plaque formation and disruption
c. Secondly it is claimed to be an link between oxidative modification of LDL and inflammatory response.
d. Both activity and mass of this enzyme can be estimated.

References

1. Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke, and mortality: *Lancet* 2010; 375: 1536–44

Patient No 73

A 45 years old woman had a blood sample sent to the lab by treating physician. No clinical details were given. No other samples were sent before or since, for comparison. Biochemistry results included the following:

- Cholesterol 0.17 mmol/L
- HDL Cholesterol 0.01 mmol/L
- Triglycerides 0.09 mmol/L
- Gamma Glutammyl Transferase 203 U/L
- ALT 68 U/L
- CK 142 U/L

a. Give ONE analytical reason for these lipid results

b. Name TWO more tests likely to be affected in this way

Write your Answers here

Answers

Patient No 73

a. Ascorbic Acid intake before the test

b. Glucose (by glucose oxidase) and Uric acid

Explanation[1]

Analytical Interference with Ascorbic Acid

a. In analytical methods with H_2O_2 generation, this problem can arise
b. In the step when peroxidase enzyme acts on H_2O_2 to produce coloured compound, ascorbic acid can compete with chromogenic substances
c. So a very high dose of ascorbic acid immediately before sample collection (as in Patient No 1) can lead to very low results of certain anlylates.
d. Ascorbic acid can also produce 'False Positive' results in urine tests for glucose or occult blood

References

1. Teitz Textbook of Clinical Chemistry and Molecular Diagnostics 5th Ed (Page 720 & 771

Liver Disorders

Patient No 74

A 42 year old female presented with jaundice, fatigue and intense pruritus, for the last 6 months. Her biochemical profile is as following:

- Bilirubin: 340 µmol/L (0-17)
- Serum total proteins: 86 g/L (65-80)
- Albumin: 31 g/L (35-50)
- ALP: 540 U/L 45-135)
- AST: 93 U/L (<42)
- GGT: 234 U/L (<38)
- Cholesterol: 7.6 mmol/L
- Viral markers: Negative
- Antimitochondrial antibodies: Positive
-

a. What is the most probable diagnosis?

b. Name ONE lipid fraction which will be most markedly raised in this patient?

Write your Answers here

Answers

Patient No 74

a. Primary Biliary Cirrhosis

b. Lipoprotein X

Explanation[1]:

a. Characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts leading to their gradual destruction and eventual disappearance

b. Autoimmune disease, 95 percent of patients with PBC are women

c. Onset is usually between the ages of 30 to 65

Clinical Manifestations:

- 50 to 60 percent of patients are asymptomatic at diagnosis
- Fatigue and pruritus are the most common.
- Cause of the pruritus in primary biliary cirrhosis is unknown
- Hyperpigmentation of skin. This change is due to melanin deposition, not jaundice.
- Musculoskeletal complaints, frequently due to an inflammatory arthropathy, occur in approximately 40 percent of patients

Laboratory Findings:

- Serum bilirubin concentration is usually normal early in the course of the disease but becomes elevated in most patients as the disease progresses. Both the direct and indirect fractions are increased

- Serum levels of aminotransferases may be normal or slightly elevated, rarely increased more than fivefold above normal
- Serum alkaline phosphatase concentration is almost always elevated in PBC, often to striking levels, and is of hepatic origin. The value tends to reach a plateau early in the course of the disease and then usually fluctuates within 20 percent of this value.
- Serum levels of 5'-nucleotidase and gammaglutamyl transpeptidase parallel those of alkaline phosphatase.
- Increased numbers of eosinophils have been demonstrated in the blood and liver
- Antimitochondrial antibodies are the serologic hallmark of PBC. They are present in about 95 percent of patients
- Antinuclear antibodies (ANA) are found in up to 70 percent of patients with PBC
- Increased serum concentrations of IgM, ceruloplasmin, bile acids (which are strikingly elevated) and hyaluronate
- <u>Hyperlipidemia:</u>
    - Hypercholesterolemia is a common feature of primary biliary cirrhosis (PBC) and other forms of cholestatic liver disease
    - Elevated VLDL and LDL levels as well as markedly elevated HDL
    - Apolipoprotein A-1 is also elevated at all stages
    - Triglyceride levels normal or slightly elevated
    - Lp(a) levels are significantly decreased
    - Excess LDL in PBC is composed of an abnormal lipoprotein particle (lipoprotein X), which is seen in cholestatic liver disease. It is rich in free cholesterol and phospholipids. Lipoprotein X is believed to reduce the atherogenicity of LDL cholesterol by preventing LDL oxidation
    - Risk of atherosclerosis in patients with PBC and hypercholesterolemia is said to be low

References

1. Clinical manifestations, diagnosis, and natural history of primary biliary cirrhosis WWW.UpToDate.com

Patient No 75

A 56 years old male has abdominal pain and mild jaundice. His biochemical profile shows:

- Albumin: 45 g/L (35-50)
- ALP: 180 U/L (30-120)
- Gamma GT: 788 U/L (<40)
- ALT: 104 U/L (<42)
- AST: 248 U/L (<35)
- Bilirubin: 36 µmol (<17)

a. What is the most probable diagnosis?

b. Name the ratio of two enzymes which can be helpful to support your diagnosis.

Write your Answers here

Answers

Patient No 75

a. Alcoholic hepatitis

b. AST/ ALT ratio (De Ritis Ratio)

Explanation[1]:

Intracellular Location of AL & AST

- ALT has mainly only one isoenzyme which is present only in the hepatocyte cytoplasm
- AST has two genetically distinct isoenzymes i.e. Cytosolic AST (cAST) and mitochondrial AST (mAST) is present in the hepatocyte cytoplasm and mitochondria respectively
- mAST is the more prevalent isoenzyme with approximately 80% of total AST activity in human liver contributed by mAST.

Biochemical Features of Alcoholic Hepatitis

- Raised AST/ALT ratio (de Ritis) is typically high in patients with severe alcoholic hepatitis and cirrhosis
- A patient with mild alcoholic hepatitis and longer elapsed period may have raised ALT.
- Raised Gamma GT is hallmark of alcoholic hepatitis

Reference

1. Mona Botros, Kenneth A Sikaris. The De Ritis Ratio: The Test of Time Clin Biochem 2013;34(11):117-130

Patient No 76

A premature neonate developed jaundice at the age of 9 days and was treated with fluorescent light. During the next week his bilirubin level dropped. After 24 hours he developed an intense grey-brown discoloration of the skin, serum, and urine. His lab investigations revealed:

- Haemoglobin : 12 g/dl
- Serum Bilirubin : 85 µmol/L
- Serum ALT : 75 U/L

a. What is most probable diagnosis?

b. What is explanation of grey-brown discoloration of skin?

Write your Answers here

Answers

Patient No 76

a. Bronze Baby Syndrome

b. Abnormal accumulation of photoisomer of bilirubin

Explanation:

- This phenomena can develop due to conversion of bilirubin into metabolites
- Bilirubin IXa can be a major contributor of this pigmentation
- Clinical importance of this phenomena is that the clinicians sometimes take it as as marker of poor prognosis

Reference

1. Mechanism of Development of Bronze Baby Syndrome in Neonates treated with Phototherapy Pediatrics 1982-Onishi-273-276

Male Reproductive System

Patient No 77

A 26 years old male is being investigated for infertility along with his female partner. He has azoospermia on semen analysis. His hormonal profile shows:

- Serum Testosterone: 987 ng/dl (260-1000)
- Serum LH: 14 mIU/ml (1-8)
- Androgen Insensitivity Index: 13,818 (<2000)
- Serum FSH: 5.2 mIU/ml (1-6)
- Prolactin: 9.7 ng/ml (5-20)

a. What is the most probable diagnosis

b. Name ONE genetic test which can be very helpful in confirming the diagnosis.

Write your Answers here

Answers

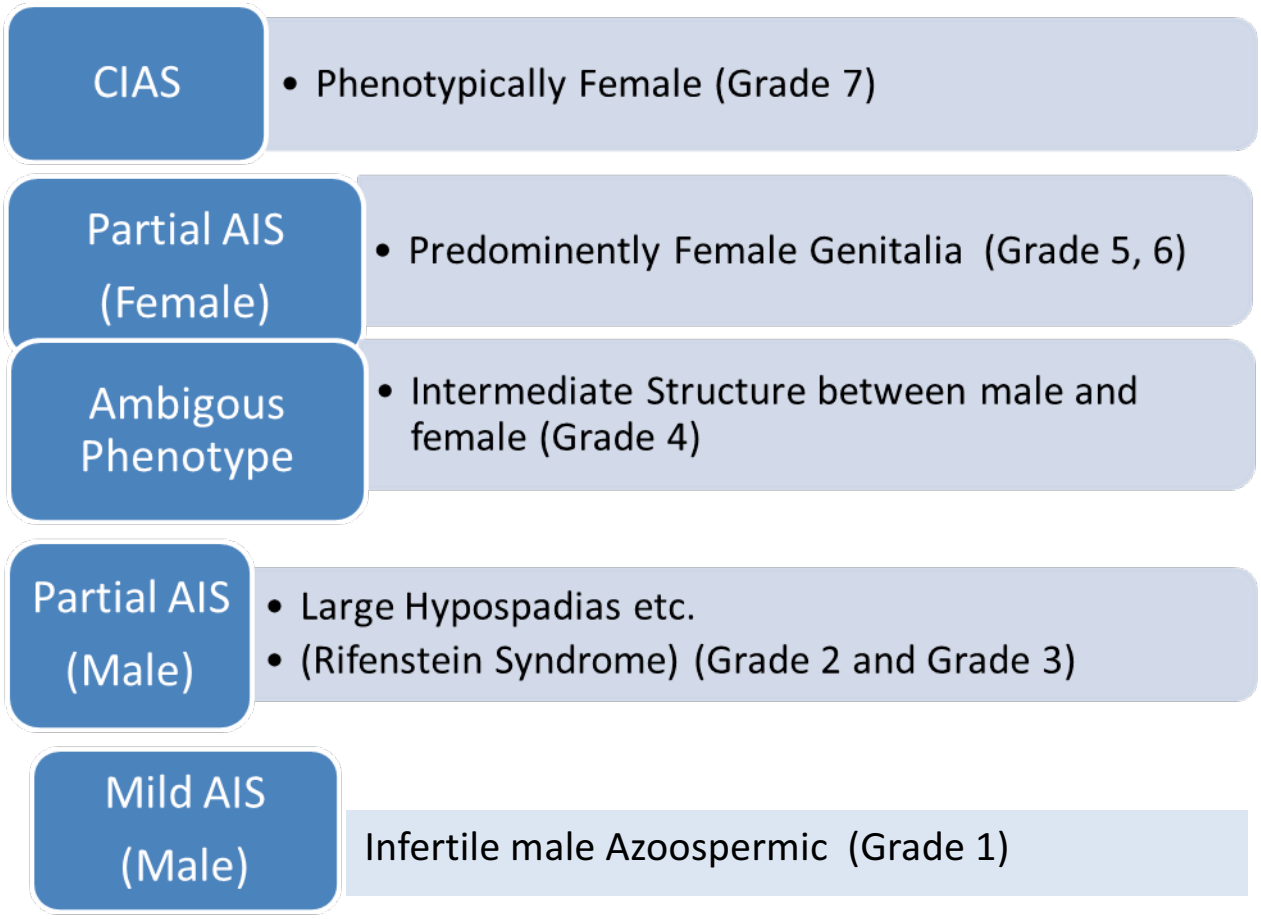
Patient No 77

a. Mild Androgen Insensitivity Syndrome

b. Androgen receptor gene defect

Explanation

- AIS is due to mutations that cause severe impairment of androgen receptor function in a 46, XY person.
- Serum testosterone concentrations is in normal range but all its actions are impaired leading to a varied phenotype depending on the severity of the disease.
- Anti-Mullarian Hormone (AMH) activity is normal so there is no uterus or tubes or only rudimentary.



Miscellaneous

Patient No 78

A 24 days old precious boy has been brought to a paediatrician with 4 days history of vomiting fever and face skin lesion. His lab investigations revealed:

- WBC Count: $10 \times 10^9/L$
- Serum CRP level: 26.0 mg/dl (<0.2 mg/dl)
- Serum ALT: 46 U/l

Physician wants to know whether this infection is bacterial or viral before start of antibiotic.

a. Name one important biochemical marker which can be very helpful in differentiating bacterial from viral infection in this patient

b. Name another biochemical marker which be helpful in differentiating gram negative from gram positive infection in this patient.

Write your Answers here

Answers

Patient No 78

a. Procalcitonin

b. Lipopolysaccharide Binding Protein

Explanation[1]

Lipopolysaccharide Binding Protein (LPBP) and Pro-calcitonin (PCN)

- Both are markers of bacterial septicaemia.
- LPBP has been claimed to be a differentiating marker for gram negative bacteria
- But recent studies have shown doubts as its role in differentiating gram positive from gram negative septicaemia.
- PCN has been shown to be a differentiating marker

References

1. A comparison of high-mobility group-box 1 protein, lipopolysaccharide-binding protein and procalcitonin in severe community-acquired infections and bacteraemia: a prospective Study. Critical Care 2007, 11:R76 (doi:10.1186/cc5967)

Patient No 79

A 20 years old female was unwell and having generalized weakness for the last three years. She also complained of chronic cough for the same duration. Her serum protein electrophoresis showed the following pattern:

• Albumin	=	39	g/L	(35-50)
• α_1 globulin	=	0.01	g/L	(1- 4)
• α_2 globulin	=	6	g/L	(3- 8)
• β globulin	=	10	g/L	(6-11)
• γ globulin	=	14	g/L	(5-17)

a. Name the clinical condition patient is suffering from

b. Name other two important clinical conditions which can present with same electrophoretic pattern

Write your Answers here

Answers

Patient No 79

a. Alpha-1 antitrypsin deficiency leading to emphysema lung

b. (1) Hepatic cirrhosis/hepatocellular carcinoma

(2) Lung cancer

Explanation

Alpha-1 Antitrypsin (AAT) Deficiency

- Emphysema of lung is the most common manifestation of AAT deficiency which results due to uninhibited action of elastase in the lung.
- Being member of the Serine Protease Inhibitors (SERPIN) family, it can also present with other manifestations
- Direct measurement of AAT can be done by techniques like immunodiffusion and nephelometry in addition to serum protein separation by Capillary Electrophoresis

References

1. Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency www.UpToDate.com

Pituitary Disorders

Patient No 80

A 29 years old male is being investigated for infertility along with his female partner. He has no history of loss of libido, impotence or galactorrhea. His routine biochemical tests were also normal. His hormonal profile revealed:

- Serum Testosterone: 755 ng/dl (260-1000)
- Serum LH: 5 mIU/ml (1-8)
- Serum FSH: 4 mIU/ml (1-6)
- Prolactin: 38 ng/ml (5-20)
- On a repeat sample similar level of prolactin was found
-

a. Name ONE important biochemical cause of high prolactin, you will like to rule out in this patient.

b. Name ONE laboratory procedure to confirm this cause.

Write your Answers here

Answers

Patient No 80

a. Macroprolactinaemia

b. Treatment of the sample with polyethylene glycol prior to analysis

Explanation[1]

- Macroprolactinaemia is the major cause of idiopathic hyperprolactinaemia.
- It is large size of prolactin formed due to complexing of an autoantibody (IgG) with prolactin
- Larger molecule remain in circulation because of poor renal excretion.
- These patients have no symptoms related to hyperprolactinaemia

Lab Detection of Macroprolactinaemia

- Lab detection of macroprolactinemia is performed by following methods:
    - Polyethyleneglycol (PEG) precipitation method
    - Gel chromatography
    - Protein A/G column
    - ^{125}I-PRL binding studies

Reference

1. Macroprolactinemia: Diagnostic, clinical, and pathogenic significance Clinical and Developmental Immunology Volume 2012, Article ID 167132, 7 pages

Patient No 81

A 34 years old female consulted her gynaecologist 8 months after the birth of her third baby because her periods had not returned since the birth. She cannot breast-feed her baby. Her laboratory tests were as following:

- Prolactin: <3 ng/mL (<29)
- FSH: 2.3 U/L (3-18)
- LH: 1.0 U/L (1.4-4.7)
- TSH: 0.25 mIU/L (0.35-4.5)
- Free T4 5.6 pmol/L (11-24)
- Cortisol (8 am) 126 nmol/L (140-700)

a. What is the most probable diagnosis in this patient?
b. What is the most important cause of this condition?

Write your Answers here

Answers

Patient No 81

a. Sheehan`s Syndrome

b. Pituitary ischaemia due to post-partal haemoorrhage

Explanation[1]

- Sheehan's syndrome is a complication of loss of life-threatening amount of blood or severe low blood pressure during or after childbirth.
- These factors can seriously damage to pituitary gland.
- Sheehan's syndrome can present with:
    - Adrenal crisis
    - Low blood pressure
    - Unintended weight loss
    - Menstrual irregularities

Reference

1. Sheehan`s Syndrome. WWW.Mayoclinic.org

Patient No 82

A 50 years old male, who had pituitary adenoma, was admitted in a hospital as he developed hypopituitarism with sudden decrease in some hormones. At this stage his lab investigations revealed:

- Serum Sodium: 121/L (132-145)

He was given some hormone replacement therapy. His sodium level is now:

- Serum Sodium: 148/L (132-145)

a. What was cause of his low sodium at admission?

b. Can you give TWO reasons of increase in his Serum Sodium in the later sample

Write your Answers here

Answers

Patient No 82

a. Cortisol deficiency secondary to ACTH def (NOT Aldosterone def)

b. 1. Glucocorticoid replacement; 2. Unmasking of Diabetes Insipidus

Explanation[1]

a. Electrolyte Changes with Treatment of Hypopituitarism

- Initial hyponatraemia was due to cortisol deficiency as a result of deficient ACTH
- Please remember it was NOT due to aldosterone def as aldosterone secretion is independent of ACTH.
- Unmasking of Diabetes Insipidus is quite interesting phenomena in this patient causing normal or increased sodium in plasma

Reference

1. Treatment of Hypopituitarism www.UpToDate.com

Patient No 83

A 34 years old female consulted her gynaecologist 8 months after the birth of her third baby because her periods had not returned since the birth. She cannot breast-feed her baby. Her laboratory tests were as following:

- Prolactin: <3 ng/mL (<29)
- FSH: 2.3 U/L (3-18)
- LH: 1.0 U/L (1.4-4.7)
- TSH: 0.25 mIU/L (0.35-4.5)
- Free T4 5.6 pmol/L (11-24)
- Cortisol (8 am) 126 nmol/L (140-700)

c. What is the most probable diagnosis in this patient?
d. What is the most important cause of this condition?

Write your Answers here

Answers

Patient No 83

a. Sheehan Syndrome

b. Post-partum haemorrhage

Explanation[1]

- Due to excessive post-partum haemorrhage pituitary infarction may occur
- One or several pituitary functions can be affected
- Failure to feed the baby may be the first sign
- Amenorrhea, hypothyroidism and hypocortisolism can also be present
- If hypotension persists even after volume restoration then serum cortisol and plasma ACTH must be tested immediately to prevent fatal adrenal crisis

Reference

1. Overview of postpartum hemorrhage www.UpToDate.com

Patient No 84

A 47 years old male suddenly presented in a hospital with severe headache, nausea and fainting. On admission he became hypotensive and required inotropic support and fluid resuscitation. His hormonal profile revealed:

- T_3 1.9 (3.4–5.6 pmol/L
- Free T_4 6.4 (9–20 pmol/L)
- TSH : 1.0 (0.3–5.5 mU/L)

A brain CT scan showed macroadenoma with probable haemorrhage.

a. What is the most probable diagnosis in this case?

b. Write THREE more endocrine tests that shall support the diagnosis (In the order of importance)?

Write your Answers here

Answers

Patient No 84

a. Pituitary Apoplexy

b. ACTH, GH, Prolactin, FSH and LH

Explanation[1]

- It is an Endocrine emergency due to haemorrhage or infarction in a pre-existing pituitary adenoma.
- Risk Factors include hypertension, medications, major surgeries, coagulopathies, or infection, head injury and radiation or dynamic testing
- The life threatening problem may be acute deficiency of ACTH and cortisol

References

1. Salam Ranabir and Manash P. Baruah Pituitary apoplexy In Endocrinol Metab. 2011 Sep; 15(Suppl3): S188–S196.

Disorders of Pregnancy

Patient No 85

A 28 year old female at 32 weeks of gestation presented with complaint of generalized itching. Her biochemical profile is:

- Bilirubin: 4.2 mg/dL (<1.0 mg/dL)
- Direct bilirubin: 2.9 mg/dL (<0.25 mg/dL)
- ALT: 86 U/L (<35 U/L)
- ALP: 840 U/L (24-125 U/L)
- GammaGT: 48 U/L (<45 U/L)
- Cholic/chenodeoxycholic acid ratio: markedly increased

a. What is the patient's likely diagnosis?

b. What is the cause of patient's generalized itching?

Write your Answers here

Answers

Patient No 85

a. Intrahepatic cholestasis of pregnancy (ICP)

b. Increased serum bile salts and accumulation of bile salts in the dermis of skin

Explanation[1]

- ICP occurs in the second and third trimester.
- It is characterized by pruritus and an elevation in serum bile acid concentrations.
- ICP occurs mainly during the third trimester when serum concentrations of estrogen reach their peak.
- ICP is also more common in twin pregnancies, which are associated with higher levels of circulating estrogens than singleton pregnancies

References

1. Intrahepatic cholestasis of pregnancy WWW.UpToDate.com 2015

Patient No 86

A 32 old years female who is pregnant for 29 weeks has developed right upper quadrant abdominal pain, nausea and jaundice. Her laboratory investigations revealed:

- Serum Bilirubin : 32 µmol/L
- ALT: 54 U/L
- AST: 87 U/L
- Serum ALP : 130 U/L
- LD: 587 U/L
- Platelet Count: 92 x 10^9 / L
- Peripheral Blood Film shows : Shistocytes (Helmet Cells)
- Urine Protein: Creatinine Ratio: 321 mg/mmol of Creatinine

a. What is the most probable diagnosis?

b. Name immune system which is most likely defective in this condition?

Write your Answers here

Answers

Patient No 86

a. HELLP Syndrome

b. The complement cascade is disturbed

Explanation[1]

Please see next patient's slides

References

1. HELLP syndrome WWW.UpToDate.com 2015

Patient No 87

A 26 years old female who is pregnant for 35 weeks has developed vomiting, epigastric pain, malaise, anorexia, and jaundice. Her laboratory investigations revealed:

- Serum Bilirubin : 32 µmol/L
- ALT: 527 U/L
- Serum ALP : 132 U/l
- Platelet Count: 129 x 10^9 /L
- Prothrombin time: Prolonged
- Glucose: 3.1 mmol/L
- Uric Acid: 439 µmol/L

a. What is the most probable diagnosis?

b. Name ONE fetal Inborn Error of Metabolism which can cause this condition in the mother

Write your Answers here

Answers

Patient No 87

a. Acute fatty liver of pregnancy (AFLP)

b. Deficiency of enzymes required for beta oxidation of Long Chain Fatty Acids of the fetus causes toxic effects on mother`s liver

Explanation[1]

HELLP and AFLP

- Both these conditions affect liver during pregnancy
- It is very difficult to distinguish the two conditions because of gross clinical and biochemical overlap.
- Generally AFLP affects liver to a greater extend as compared to HELLP
- Please see the table ***"Clinical characteristics of liver diseases in pregnancy"*** in the next slide

References

1. Acute Fatty Liver Disease of Pregnancy WWW.UpToDate.com 2015

Patient No 88

A 42 years old female has been referred to you by a Fertility Clinic for assessment of ovarian reserve before planning an ICSI procedure. The results of her hormonal tests were as following:

Day 3 of Regular Menstrual Cycle:

FSH : 8 mIU/ml

Oestradiol : 67 pg/ml

Clomiphene Citrate Challenge Test

Day 3 FSH: 9.6 mIU/ml

Day 10 FSH: 10.9 mIU/ml

Day 3 Oestradiol: 71 pg/ml

a. What is your opinion about the Ovarian Reserves in this patient?

b. Name one lab test that will be helpful in confirmation of the diagnosis?.

Write your Answers here

Answers

Patient No 88

a. Good ovarian reserve

b. Anti Mullarian Hormone (AMH).

Explanation[1]

Assessment of Ovarian Reserve

- Chemical Pathologist may be required to carry out investigations related to ovarian reserve.
- These patients are referred from Fertility Clinics for selection of patients for procedure like ICSI.
- The tests done are :
    - Day 3 FSH (should be <10 mIU/ml) and oestradiol (< 80 pg/ml)
    - Similar values after Clomiphene Citrate Challenge Test
- AMH is an excellent marker of ovarian reserve.
- AMH >1.0 ng/mL but <3.5 ng/mL suggests a good response to stimulation

References

1. Evaluation of female infertility WWW.UpToDate.com 2015

Patient No 89

A 37 years old female underwent a Second Trimester Quadruple Screening test with following results:

- Beta HCG: 2.3 Multiple of the Median (MoM) (High)
- Alpha Fetoprotein: 0.67 MoM (Low)
- Unconjugated Oestriol : 0.75 MoM (Low)
- Inhibin A: 2.4 MoM (High)

a. Name ONE most important fetal anomaly you would like to exclude in this patient by invasive tests

b. Name ONE more maternal blood test based on nucleic acid, which can be used in this patient for screening of fetal anomalies

Write your Answers here

Answers

Patient No 89

a. Down Syndrome

b. Cell free DNA in maternal serum

Explanation[1]

- Maternal Serum Screening are the blood test offered to pregnant women who want to find out if they may be at increased risk of having a baby with disease like Down syndrome, neural tube defects (such as spina bifida) or Trisomy 18 and many others
- They can be carried out in the first or second trimester
- Following biochemical tests are included:
    - Beta HCG
    - Alpha fetoprotein
    - Unconjugated Oestriol
    - Inhibin A
    - Pregnancy Associatd Plasma Protein A (PAPPA)

References

1. Laboratory issues related to maternal serum screening for Down syndrome WWW.UpToDate.com 2015

Renal Disorders

Patient No 90

An 18 years olds male presents with acute gouty arthritis and renal functional impairment (see below). He has strong family history of gout and Chronic Kidney Disease starting during teen age. His lab investigations are as following:

- Uric Acid: 678 µmol/L
- Creatinine: 345 µmol/L
- Urine albumin: 2.1 mg/mol of creatinine (<3)
- Urine Microscopy: Negative
- Fractional Excretion of Uric Acid: 3.2 % (ref values: 5-11%)
- Uromodulin gene (UMOD) mutation: Positive

a. What is the most probable diagnosis?

b. What is the older name of Uromodulin

Write your Answers here

Answers

Patient No 90

a. Uromodulin Kidney Disease (UKD)

b. Tom-Horsefall protein

Explanation[1,2]

Uromodulin

- In physiological range it is the most abundant urinary protein
- Previously called Tamm– Horsfall protein, is expressed exclusively by the thick ascending limb cells of the kidney and released into urine from the apical cell membrane.
- It is supposed to be a protective factor for UTI and renal stones
- Recently other functions have also been reported

Uromodulin function

- Urothelial defence against infections
- Urothelial defence against calcium oxalate crystals-induced damage
- Urothelial defence against ischemic damage
- Water / salt balance in TAL and DCT

Uromodulin Kidney Disease (UKD)

- Also called Uromodulin Associated Kidney Disease (UAKD)
- Group of comprising 3 mutually non-exclusive disorders :
    - Medullary cystic disease type 2,
    - Familial juvenile hyperuricemic nephropathy
    - Glomerulocystic kidney disease.

Diagnosis of UKD

- UKD should be suspected in a patient in late teens or in 20`s with:
    - Hyperuricaemia or gout

- CKD
- Strong family history of gout and/or CKD (as UKD is mostly autosomal dominant)
- Fractional Excretion of Uric Acid : < 4%
- Final diagnosis is by mutation analysis
- Assays for Uromodulin (by ELISA) are not yet commercially available.

References

1. Autosomal dominant tubulointerstitial kidney disease (medullary cystic kidney disease) www.UpToDate.com 2015

2. Uromodulin: old friend with new roles in health and disease Pediatr Nephrol (2014) 29:1151–1158

Patient No 91

A 62 years female is a known diabetic for the last 10 years. She is feeling lethargy and has course skin and bradycardia. Serum Cystatin C was advised for early detection of diabetic nephropathy.

Her biochemical reports showed:

- Serum Cystatin C : 0.88 mg/l (0.63–1.33)
- Urine albumin : creatinine ratio: 23.1 mg/mmol (<3.5)

a. What is the most probable cause of this discrepancy?

b. Name ONE lab investigation which can be helpful to resolve this issue.

Write your Answers here

Answers

Patient No 91

a. Cystatin C is not a good marker in patients with thyroid disorders

b. TSH

Explanation[1]

- Cystatin C is claimed to be a superior marker of kidney function as compared to creatinine.
- It is filtered solely by the glomerulus.
- It is not handled by the renal tubules, and is generated at a constant rate by all cells in the body.
- It has been studied as part of eGFR formulae.
- Cystatin C has two limitations :
    - Thyroid disorders (both hypo- and hyperthyroidism)
    - Glucocorticoid therapy

References

1. Cystatin C and Its Role in Patients with Type 1 and Type 2 Diabetes Mellitus Alaaeldin M. Bashier, Puja Murli Thadani, Ayman Aly Seddik Fadlallah, Elamin Abdelgadir, Nada Alhashemi, and Fauzia Rashid Advances in Endocrinology Volume 2015, Article ID 254042

Patient No 92

A 57 old male has BMI 31 Kg/m^2. His serum creatinine remains mildly elevated. Laboratory has reported following two eGFR reports:

- eGFR (by MDRD) : 69 ml/min
- eGFR (by CKD-EPI) : 78 ml/min

a. Which eGFR result you will prefer to accept?

b. Give TWO reasons for your selection.

Write your Answers here

Answers

Patient No 92

a. eGFR (by CKD-EPI)

b. This eGFR equation is valid throughout the range of GFR, mild to moderate impairment. Secondly it is more appropriate in obese persons.

Explanation[1]

- eGFR formulae are based on serum or plasma creatinine. Urine sample NOT required
- They take into account age, gender, ethnicity and BMI of the patient.
- Three formulae are used:
    1. Cockcroft and Gault: requires BMI.
    2. MDRD: Not suitable for mild CKD and in obese patients
    3. CKD-EPI: Suitable throughout the CKD range.

References

1. Christopher M Florkowski, Janice SC Chew-Harris Methods of Estimating GFR – Different Equations Including CKD-EPI Clin Biochem Rev Vol 32 May 2011

Patient No 93

An 11 months old male infant presented with vomiting and failure to thrive since birth. He also had polyuria and polydipsia. His length and weight were < 3rd percentile. His biochemical investigations revealed:

- pH: 7.24 (7.35 - 7.45)
- PCO_2: 20 mmHg (35 – 45)
- HCO_3 : 12.2 mmol/L (20 – 28)
- Chloride: 121 mmol/L (96 -104)
- Anion gap: 6.3 (8 -16)
- Plasma glucose (R) 5.8 mmol/L (5.6-6.9)
- Serum potassium : 2.2 mmol/L (3.6–5.2)
- Serum Phosphorous: 0.54 mmol/L (0.98 -1.65)
- Urine pH: 5.0
- Urine Glucose: +++
- Urine Amino acids (By HPLC): Several Amino acids present
- Urine K:Creat Ratio: 4.3

Name TWO important conditions present in this infant

Write your Answers here

Answers

Patient No 93

a. Fanconi Syndrome and Renal Tubular Acidosis (Type 2)

Explanation[1]

- Fanconi Syndrome, Cystinosis and RTA Type 2, all these condition may co-exist in an infant
- Cystinosis is the initial culprit which is a lysosomal storage disease. It starts with the failure of transport cystine out of the lysosomes leading to damage of the cells
- This leads to increased excretion of many substances in the urine e.g. glucose, phosphorous, several amino acids and potassium
- Failure to regenerate HCO_3 leads to type 2 (proximal) RTA

References

1. Cystinosis: Practice Guidelines and Diagnosis www.Medscape.com

Patient No 94

A 50-year-old woman had increasing malaise for the past 6 months. She is a known diabetic for the last 9 years. She is afebrile and normotensive. Laboratory studies show:

- Serum creatinine: 4.5 mg/dl
- Urea: 134 mg/dl
- Glucose 230 mg/l
- Hemoglobin A1C 7.9 %.

Urine

- Albumin : Creatinine Ratio: 450 mg/g of creatinine

a. Name renal pathology causing diabetic nephropathy in this patient?

Write the new terminology used for the albuminuria present in this patient.

Write your Answers here

Answers

Patient No 94

a. KimmelstielWilson lesion

b. Severely increased albuminuria, formerly called macroalbuminuria" (defined as urinary albumin excretion above 300 mg/day or above 30 mg/g creatinine on a random urine sample).

Explanation[1]

- Various stages of Diabetic Nephropathy have been described
- Urine albumin Creatinine ratio is now a widely used test for early detection
- Microalbuminuria (3.4-34 mg/mmol of creatinine) is now called **'Moderately Increased Albuminuria'.**
- Microalbuminuria (> 34 mg/mmol of creatinine) is now called **'Severely Increased Albuminuria**

References

1. Overview of diabetic nephropathy www.UpToDate.com 2015

Patient No 95

A 76-year-old woman was admitted to a geriatric ward for assessment. She was not on any medication and there was no suggestion of diabetes mellitus. Plasma and urinary electrolyte estimation revealed:

• pH:	7.32		
• HCO_3	20	mmol/L	(23 – 33)
• Na^+	134	mmol/L	(132 – 144)
• K^+	6.2	mmol/L	(3.2 – 4.8)
• Cl	112	mmol/L	(98 – 108)
• Creatinine	230	µmol/L	(60-120)
• Urea	9.5	mmol/L	(3.0-8.0)
• Anion Gap	8	mmol/L	(7-17)
• Renin activity	0.1	ng/mL/h	(0.1-0.4)
• Aldosterone	4.5	ng/L	(10-150)

a. What is the most probable diagnosis?

b. Write TWO causes of this disorder

Write your Answers here

Answers

Patient No 95

a. Type IV RTA

b. Hyporeninaemic Hypoaldosterone and Diabetes mellitus

Explanation[1]

- RTA type IV is characterized by metabolic acidosis and hyperkalaemia (as opposed to hypokalaemia in other types)
- Causes:
    - Hyporeninemic Hypoaldosteronism
    - Diabetic nephropathy
    - NSAIDS
    - Calcineurin inhibitors
    - ACE inhibitors and ARBs
    - Heparin and LMW heparin
    - Adrenal insufficiency

References

1. Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA) www.UpToDate.com 2015

Patient No 96

A 28 year old male victim of earthquake received multiple injuries including a large haematoma of right thigh about 24 hours ago. His biochemical test values are as following:

Serum:

- Na^+ 140 mmol/L (138-145 mmo/L)
- K+ 6.3 mmol/L (3.5-5 mmo/L)
- Cl^- 100 mmol/L (95-105 mmol/l)
- Urea 20.4 mmol/L (2.5-7.7 mmol/l)
- Creatinine 493 µmol/L (50-120 µmol/l)
- HCO3: 15 mmol/lL (22-28 mmol/L)

Urine

- Fractional Excretion of Na+: 0.78 %
- Urine osmolality: 350 mosm/lKg
- Urine output:: 300 ml/24 h

a. What is the diagnosis?

b. Write TWO reasons of elevated serum potassium in this patient

Write your Answers here

Answers

Patient No 96

a. Acute Kidney Injury (due to rhabdomyolysis)

b. Renal failure, tissue damage and metabolic acidosis

Explanation[1]

- Victims of earthquake are very much prone to rhabdomyolysis leading to AKI
- Characteristic biochemical features include high CK and myoglobinuria (not mentioned in the patient in scenario).
- The most unique feature is low Fractional Excretion of Sodium, which is high in other causes of ATN but <1% in this condition.
- The hallmark of treatment is flushing the patient with intravenous fluids even before evacuation, if possible.

References

1. Crush related acute kidney injury WWW.UpToDate.com

Therapeutic Drug Monitoring

Patient No 97

A 45 years old man is brought to the emergency by his wife. He has ingested some unknown medication in a suicide attempt. The patient is disoriented in time. His temperature is 103^0 F, blood pressure is 120/85 mmHg, pulse is 100/ min (irregular) and respiration ate is 22/min. The skin is flushed and dry. Dilated pupils and muscle twitching are also noted on physical examination. ECG reveals prolonged QRS complexes. :

- Serum ALT : 24 U/L
- Arterial Blood Gases: normal acid base status.

a. Name the drug which is the most likely cause of intoxication?

b. Name the analytical technique used to confirm the presence of the drug in the blood.

Write your Answers here

Answers

Patient No 97

a. Tricyclic antidepressant (TCA)

b. Liquid Chromatography-Mass Spectrometry (LC-MS)

Explanation[1]

- TCA are still an important cause of suicidal poisoning.
- Cardiovascular effects of TCA toxicity are important, which resemble an anti-arryhthmic drug like decreases conduction velocity, increase duration of repolarization, and prolonged absolute refractory periods
- Decreased level of consciousness or delirium may be present.
- Management is usually started on clinical presentation.
- For final diagnosis LC-MS is used. With this technique we can measure almost 8 TCA compound

References

1. Tricyclic antidepressant poisoning www.UpToDate.com 2015

Thyroid Disorders

Patient No 98

A 45 years old male was clinically euthyroid without any visible goiter. Following are the results for thyroid function tests. The patient recalled that his father also had some 'abnormal' thyroid tests but had never been investigated further.

- Total T4: 280 nmol/L (60-160)
- Free T4: 14.5 pmol/L (8-21)
- TSH: 3.2 mIU/L (0.4-4.5)
- T3 resin uptake: 29% (25-35%)
- Free Thyroxine Index: 629 (50-150)

a. What is the most likely diagnosis?

b. What treatment does he require for this condition?

Write your Answers here

Answers

Patient No 98

a. Familial dysalbuminemic hyperthyroxinemia —*(Answers with similar annotation should be acceptable)*

b. Benign condition does not require any specific treatment

Explanation[1]:

- With the use of Free T3 and Free T4 assays, the problem of binding protein are rarely seen
- T3 Resin Uptake and Free Thyroxine Index (FTI) were two parameters used concomitantly with total assays.
- T3Resin Uptake will be normal but FTI will be increased.
- FTI is calculated as following:

  T3 Resin Uptake X Total T4

- In a male with family history the most probable cause is Familial dysalbuminemic hyperthyroxinemia

Reference

1. Euthyroid hyperthyroxinemia and hypothyroxinemia www.uptodate.com ©2015

Patient No 99

A 47 years old male is having tachycardia but no other clinical features of thyrotoxicosis. His thyroid hormonal profile shows:

- Free T4 : 46 pmol/L (6-21)
- Total T3 : 5.8 nmol/L (1.1-2.7)
- TSH: >81 mIU/L (0.4 -4.0)

a. What is the most probable diagnosis?

b. Name the genetic defect most likely to be present in this patient.

Write your Answers here

Answers

Patient No 99

a. Resistance to Thyroid Hormones Beta

b. Defect of beta thyroid receptors

Explanation[1]:

- Reduced response of thyroid tissues to thyroid hormones
- T_3 and T_4 are raised
- TSH may be raised or normal

Two types:

- RTH Beta: in which beta receptors are defective
- RTH Alpha: Much rarer than beta
- In cardiac tissue mostly alpha receptors are present, so palpitation may be found in RTH beta.

Reference

1. Impaired sensitivity to thyroid hormones. www.uptodate.com ©2015

Patient No 100

A 3 days old infant underwent newborn screening in a developed country with following result:

TSH: 3.3 mIU/L

After first month he developed symptoms and signs suggestive of Hypothyroidism and later investigations confirmed it.

a. What is the most probable reason of failure to detect this hypothyroidism by the screening programme? (No lab errors assumed).

b. What improvement you will suggest in the screening programme to avoid this failure.

Write your Answers here

Answers

Patient No 100

a. Central Hypothyroidism

b. TSH and T4 measurement simultaneous

Reference

1. Clinical features and detection of congenital hypothyroidism. WWW.UpToDate.com 2015

Patient No 101

A newborn was tested for Serum TSH 12 hours after birth in a country where “Newborn Screening Programme” does not exist. The result was:

Serum TSH: 33.3 mIU/L

The Paediatrician immediately started replacement therapy with an appropriate dose of thyroxine to avoid developmental loss of IQ. Thyroid function tests carried out a month later indicated severe hyperthyroidism in the baby i.e. Very Low TSH and high T4. Baby became alright on stopping the replacement therapy.

Write TWO important causes of this discrepancy. (No analytical error assumed)

Write your Answers here

Answers

Patient No 101

a. During first 24 h of life TSH can be normally very high

b. Transient hypothyroidism

Explanation[1]:

Approaches of Newborn Screening for CH

- Two approaches for Newborn Screening of CH:
    - T4/follow-up TSH
    - TSH/follow-up T4
- Major disadvantage of T4/follow-up TSH approach is missing of Sub-clinical Hypothyroidism which is quite common
    - So more institutes are adopting TSH/follow-up T4 now

Central CH

- Infants with central (hypothalamic or pituitary) hypothyroidism are detected by screening programs that employ the initial T4/follow-up TSH approach.
- Programs based only on TSH screening alone will not identify these infants.
- In Central CH, TSH may be low or low normal.

Timing of the TSH Test

- Serum TSH concentrations rise abruptly to 60 to 80 mIU/L, typically peaking 30 minutes after birth.
- The serum TSH concentration then decreases rapidly to about 20 mIU/L, 24 hours after delivery, and then more slowly to 6 to 10 mIU/L at one week of age.
- A serum TSH >10 mIU/L is definitively elevated in infants after one week of age.

Transient Hypothyroidism

- Iodine Deficiency
- Transplacental transfer of TSH-receptor blocking antibodies (TRB-Ab) can occur in infants of mothers with autoimmune thyroid disease
- Antithyroid drugs – Antithyroid drugs given to mothers with hyperthyroidism also can cross the placenta.
- Iodine exposure – Exposure of the fetus or newborn to high doses of iodine can cause hypothyroidism.
- Large haemangioma of the liver
- Genetic defects

Reference

1. Clinical features and detection of congenital hypothyroidism. WWW.UpToDate .com 2015

Patient No 102

A 30 year old male complains of frequent attacks of leg muscles pain and stiffness followed by weakness. He also has anxiety, tachycardia, weight loss and excessive sweating. His lab investigations revealed:

- Bicarbonate 27 mmol/L (22-28)
- Na 142 mmol/L (138-145)
- K 2.3 mmol/L (3.5 - 5.0)
- Chloride 101 mmol/L (95-105)
- Urine K 6.1 mmol/l

a. Give TWO most important differential diagnosis in this patient

b. Name ONE hormone test which can be very helpful in differentiating these two conditions

Write your Answers here

Answers

Patient No 102

a. Familial Periodic Paralysis and Thyrotoxic Periodic Paralysis

b. TSH

Explanation[1]

- Hereditary (Familial) Periodic Paralysis and Thyrotoxic Periodic Paralysis
- The prevalence of thyrotoxic PP is high in in Asian males
- Increases sodium-potassium ATPase activity on the skeletal muscle membrane is at possible cause
- Hyperinsulinaemia due to insulin resistance is also reported in thyrotoxic PP.

Reference

1. Thyrotoxic periodic paralysis www.uptodate.com ©2015

Uric acid Disorders

Patient No 103

A 51 years old male develops pain, swelling and redness on his right big toe. His laboratory investigations revealed:

- TLC: 12 x 109/L
- ESR 92 mm after 1st hour
- Uric Acid: 234 µmol/L

Treating physician has sought your opinion regarding the diagnosis of gout in this patient.

a. Name the test and the likely finding which can confirm gout in this patient.

b. When serum uric acid should be repeated in this patient to obtain a meaningful result?

Write your Answers here

Answers

Patient No 103

a. Monosodium Urate crystals in joint aspirate which give negative birefringence on polarized microscopy.

b. At least 2 weeks after the symptoms are over

Explanation[1]

- Uric acid level can be misleading in the diagnosis of gout
- Monosodium urate (MSU) crystals found in joint fluids is the final test
- MSU can be visualised by polarized microscope
- An important D/D is Calcium Pyrophosphate (CPP) arthritis

References

1. Clinical manifestations and diagnosis of gout www.UpToDate.com 2015

Patient No 104

A 45 years male is a known patient of Chronic Kidney Disease (CKD). His BP is 165/105 mmHg. He has following biochemical findings:

- Urea: 27.8 (3.3-6.7 mmol/l)
- Creatinine: 874 (55-100 µmol/l)
- Uric Acid: 512 (120-420 µmol/l)
- Triglycerides 4.3 (<1.87 mmol/L)

a. Which category of hyperuricaemia this patient is suffering?

b. Name ONE drug which can be most helpful in this patient.

Write your Answers here

Answers

Patient No 104

a. Secondary Hyperuricaemia due to renal failure

b. Losartan (Angiotensin Receptor blocker)

Vitamin and Mineral Disorders

Patient No 105

A 10 years old male child presented with alopecia, ophthalmic disorders, diarrhea, severe growth retardation, delayed sexual maturation, neuropsychiatric manifestations, and frequent infections. Scaly erythematous plaques were observed over hands, feet, anogenital area and around mouth. His lab tests revealed the following:

- Bilirubin: 20 µmol/l (3-17)
- Albumin : 30 g/L (35-50)
- ALT: 225 U/L (<42)
- ALP: 15 U/L (30-120)
- GGT: 56 U/ L (< 45)

a. What is the clinical diagnosis?

b. What is the single most important biochemical test you would advise to confirm this diagnosis?

Write your Answers here

Answers

Patient No 105

a. Acrodermatitis Enteropathica (Zinc Deficiency)

b. Serum Zinc Level

Explanation[1]

a. Acrodermatitis Enteropathica is an autosomal recessive disease in which zinc absorption is impaired

b. Mutations in the SLC39A4 gene on chromosome 8q24.3, which encodes a protein that appears to be involved in zinc transportation

c. Clinical Manifestations: Alopecia, ophthalmic disorders, diarrhea, severe growth retardation, delayed sexual maturation, alopecia, neuropsychiatric manifestations, and frequent infections. Scaly erythematous plaques over hands, feet, anogenital area and around mouth

Other Causes of Zn Deficiency

a. Dietary zinc depletion due both inadequate zinc intake and the binding of ingested zinc to fiber and phytates

b. Zinc absorption may be impaired in pancreatic disease or insufficiency. Pancreatic enzymes are necessary for release of dietary zinc

c. Breastfeeding

d. Crohn's disease, Cystic fibrosis, sickle cell disease, liver disease and renal disease.

Low ALP in Zinc Deficiency

a. ALP may be markedly reduced in Zinc Def.

b. This finding may be very important for a Chemical Pathologist, who attribute such a finding to 'analytical error'

c. Calcium, Magnesium and Phosphorus may also be low.

d. Zn estimation is best carried out on Atomic Absorption Spectroscopy

References

1 Zinc deficiency negatively affects alkaline phosphatase and the concentration of Ca, Mg and P in rats

2. Clinical manifestations, diagnosis, and natural history of primary biliary cirrhosis WWW.UpToDate.com

Patient No 106

A 71 years old male is admitted in hospital for the last one week for the investigations of pancytopaenia and hypersegmented neutrophils. He is on special hospital diet. His MCV is 80 fL. His relevant biochemical profile shows:

- Serum Vitamin B12: 220 pmol/L (Normal > 221)
- Serum Folate: 9.0 nmol/L (Normal > 9.1)
- Serum Homocystine: Raised
- Urine Methylmelonic Acid: Raised

a. What is the most likely diagnosis?

b. Name ONE lab investigation which can be helpful to obtain a better status of folate in this patient.

Write your Answers here

Answers

Patient No 106

a. Vitamin B12 deficiency

b. Red cell folate

Explanation[1]

Lab Diagnosis of Vitamin B12 Def

- Normal: >300 pg/mL (>221 pmol/L)
- Borderline:200 to 300 pg/mL (148 to 221 pmol/L)
- Vitamin B12 Def: <200 pg/mL (<148 pmol/L)

For Borderline cases:

- Homocyctine raised but normal methylmelonic acid: Folate Deficiency
- Homocyctine and methylmelonic acid: B12 Def

Serum or Red Cell Folate

- The serum folate concentration are unequivocally low in patients with folatedeficient megaloblastic anemia but it be falsely normal in some situations e.g. diet with sufficient folates.
- Pregnancy, alcohol intake, certain anticonvulsants, or a few days of decrease dietary intake can lower the serum folate concentration, despite the presence of adequate tissue stores.
- Red cell folate is free of short time fluctuations and is, therefore, a better indicator of folate status
- Some studies have, however, questioned routine use of red cell folate estimation

References

1. Diagnosis and treatment of vitamin B12 and folate deficiency www.uptodate.com ©2015

Patient No 107

A 31years old female is a newly diagnosed patient of pulmonary tuberculosis. She is being evaluated for her anaemia before start of the anti-tuberculosis treatment. Her lab investigations show:

- Hamoglobin: 7.9 g/dl
- Serum ferritin: 110 ng/ml
- Hepcidin : Increased
- Soluble Transferrin Receptors: Increased

a. Comment on Iron Status of the patient

b. Write ONE probable cause of raised hepcidin in this patient

Write your Answers here

Answers

Patient No 107

a. Iron Deficiency is present

b. Hepcidin is an acute phase reactant, so it is raised in this patient

Explanation[1]

New Markers of Iron Deficiency (ID)

- Ferritin is a sensitive marker for ID but it is also a positive acute phase reactant (APR).
- So ferritin is not a good marker of ID in patients with inflammation as it can be falsely normal
- Hepcidin is also an APR and can be falsely high in spite of low iron

Soluble Transferrin Receptors (sTfR)

- sTfR has the advantage that it is not effected by inflammation
- This is the protein which is shed from maturing reticulocytes in the circulation
- It is increased in ID
- It indicates Stage II (Iron Deficient Erythropoiesis) and Stage III (Insufficient Iron Supply) of ID, so is a 'dual indicator'

Patient No 108

A 31 year old man who is a heavy ethanol user presents with 3 week history of dyspnoea on effort, ankle swelling, parasthesiae of feet. On examination he has confusion, ataxia, and nystagmus, bilateral pedal oedema and warm periphery. Motor power is normal. His laboratory investigations revealed:

- Urea: 4.2 mmol/L (3.2-6.5)
- Creatinine: 100 µmol/L (75-117)
- Albumin: 25 g/L (30 – 50)
- Ca^{2+} 2.0 mmol/L (2.1 - 2.6)
- Total bilirubin 15 µmol/L (<17)
- AST: 60 U/L (< 40)
- Gamma GT 120 U/L (< 50)
- Serum B12: Normal
- RBC transketolase Decreased

a. What is the most probable diagnosis in this patient?

b. What is the most important cause of this condition?

Write your Answers here

Answers

Patient No 108

a. WernickeKorsakoff Syndrome

b. Vitamin B1 Deficiency

Explanation[1]

- Two distinct syndromes
    - Acute/subacute confusional state and often reversible findings of Wernicke encephalopathy
    - Persistent and irreversible findings of Korsakoff dementia
- A deficiency of thiamine (vitamin B1) is responsible for the symptom complex.

References

1. Wernicke-Korsakoff Syndrome: Background, Etiology, Pathophysiology

   Medscape Reference

Patient No 109

A 78 y old man has been referred to you by your Hematologist colleague with following laboratory test results with a question mark on the analytical accuracy of your B12 result

- Haemoglobin: 8.4 g/dl
- MCV : 68 fl/L (62-78)
- Serum B12 Level: 104 ng/ml (206-678)
- Plasma Homocysteine: Raised
- Plasma Methylmelonic Acid : Raised

a. What is most probable cause of his MCV result

b. Name ONE biochemical investigation to support your diagnosis

Write your Answers here

Answers

Patient No 109

a. Concomitant Vitamin B12 and Iron Deficiency

b. Serum Ferritin

Explanation[1]

Concomitant B12 and Ferritin Deficiency

- Presence of Iron Def along with B12 deficiency may mask the macrocytosis
- MCV may be <80 fl in spite of B12 deficiency
- In such cases serum ferritin may be carried out and if Iron Def is also present it must be treated along with B12
- Serum concentrations of homocysteine as well as serum and urinary concentrations of methylmalonic acid are elevated in vit b12 def. In folic acid deficiency only homocysteine is increased

References

1. **Diagnosis and treatment of vitamin B12 and folate deficiency** www.UpToDate.com

Patient No 110

A 21 years old male has slow and slurred speech which is difficult to understand, abnormal gait, tremors nausea and decreased appetite. He is also under treatment of a psychiatrist due to mental illness. He has been referred to you for the diagnosis (or exclusion) of Wilson's disease. His ophthalmic examination and investigations were as following:

- Eye examination: Kayser-Fleischer rings Present
- MRI Brain: Findings suggestive of Wilsons Disease.
- Serum Bilirubin : 48 µmol/L
- Serum ALT : 245 U/L
- Serum Ceruloplasmin: 226 mg/L
- Serum Non-Ceruloplasmin Copper: 165 µg/L
- 24 h Urine Copper: 84 µg
- Urine Copper after Penicillamin Challenge Test: 956 µg

a. Based on the results of most of these Biochemical Tests will you support the diagnosis of Wilson's disease in this patient?

b. Can you name a biochemical test along with its method which can be helpful in reaching the final diagnosis?

Write your Answers here

Answers

Patient No 110

a. No; most biochemical features do not support the diagnosis of WD.

b. Ultrfilterable free Copper estimation

Explanation[1]

- Biochemical features of WD include following:
    - Low Ceruloplasmin
    - Increased non-cruloplasmin Cu (Cu index)
    - Increased Urinary Cu
    - High Urine Cu after Penicillamin challenge
- Gold Standard is Liver Cu content determined by liver biopsy
- Estimation of free Cu after Ultrafilteration has been described as an accurate and precise method.

References

1. **Direct Measurement of Free Copper in Serum or Plasma Ultrafiltrate**

   www.medscape.com

Water & Electrolyte Disorders

Patient No 111

A 55 year old male has cough and haemoptysis for the last one year. He is also having diarrhoea for the last one day.

Results of his biochemical tests are as following:

- Na: 118 mmol/L (132-144)
- K: 4.4 mmol/L (3.2-4.8)
- Urea: 4.3 mmol/L (3.6-6.7)
- Creatinine: 83 µmol/L (60-95)
- Glucose (F): 5.3 mmol/L (<5.6)

a. Write TWO most important differential diagnosis in this patient

b. Name ONE simple, commonly available test which can be used to differentiate the two conditions.

Write your Answers here

Answers

Patient No 111

a. SIADH and Hypovolumic Hyponatraemia

b. Urine Sodium

Explanation[1]

- SIADH or SIAD and hypovlumic hyponatraemia (as occurs in intestinal loss of sodium-rich fluid) are both conditions of hyponatraemia
- SIADH is a condition of volume expansion, therefore, a signal of urinary sodium loss in initiated causing 'increased urine sodium excretion'.
- In Hypovolumic Hyponatraemia a normal kidney will conserve sodium (Low Fractional Excretion of Sodium).
- So a simple test like urine sodium can be very helpful in this patient

References

1. Disorders of Plasma Sodium — Causes, Consequences, and Correction **N Engl J Med 2015;372:55-65. DOI: 10.1056/NEJMra1404489**

Patient No 112

A 19 years old female has been suffering from generalized weakness and weakness in legs for the last 3 years. There is no history of diarrhoea or vomiting. On examination the patient looks emaciated. Her lab investigations revealed:

- pH : 7.49 (7.35-7.45)
- Na : 140 mmol/L (135-150)
- K : 2.6 mmol/L (3.5-5.0)
- Cl : 100 mmol/L (98-106)
- HCO3 : 38 mmol/L (22-28)
- Urea : 4.9 mmol/L (3.3-6.7)
- Creatinine : 82 µmol/L (62-115)
- Urinary Potassium: 76 mmol/day (22-57)
- Plasma Aldosterone: Raised
- Plasma Renin Activity: Raised

a. Give TWO most important differential diagnosis

b. Name ONE laboratory test which can be very helpful in differentiating these two conditions.

Write your Answers here

Answers

Patient No 112

a. Barter Syndrome and Gitelman syndrome

b. Urinary Calcium concentration

Explanation[1]

a. Autosomal recessive disorders

b. Hyperplasia of the juxtaglomerular apparatus

c. Secondary Hyperaldosteronism and Hyperreninism

d. Metabolic Alkalosis

e. Hypokalaemia

f. Increased Urinary Potassium

g. Hypomagnesemia (in some patients)

Differences between Barter Syndrome and Gitelman Syndrome

Barter Syndrome	Gitelman syndrome
Infant and Young Children	Adults (sometimes late childhood)
Growth and mental retardation	Polyuria and polydipsia alongwith fatigue and weakness
Urinary Calcium Excretion: Increased	Urinary Calcium Excretion: Low or Normal
Mimics Loop Diuretic action	Mimics Thiazide Diuretic action
1 in 1,000,000 (less common)	1 in 40,000 (Much more common)
Impairment in one of the transporters involved in sodium chloride reabsorption in the loop of Henle	Impairment in one of the transporters involved in sodium chloride reabsorption in the distal tubule
Blunted response to a loop diuretic	Blunted response to a thiazide diuretic
Urine concentrating ability is impaired	Urine concentrating ability relatively preserved
Urinary PGE2 excretion increased: so NSAIDS are important part of treatment alongwith K sparing diuretics	Urinary PGE2 excretion appears to be normal: so NSAIDS are of no use and K sparing diuretics are the only treatment

References

1. Barter Syndrome and Gitelman Syndrome www.uptodate.com ©2015

Patient No 113

A 30 year old male complains of frequent attacks of leg muscles pain and stiffness followed by weakness. He also has anxiety, tachycardia, weight loss and excessive sweating. His lab investigations revealed:

- Bicarbonate 27 mmol/L (22-28)
- Na 142 mmol/L (138-145)
- K 2.3 mmol/L (3.5 - 5.0)
- Chloride 101 mmol/L (95-105)
- Urine K 6.1 mmol/l

a. Give TWO most important differential diagnosis in this patient

b. Name ONE hormone test which can be very helpful in differentiating these two conditions.

Write your Answers here

Answers

Patient No 113

a. Familial Periodic Paralysis and Thyrotoxic Periodic Paralysis

b. TSH

Explanation[1]

- Hereditary (Familial) Periodic Paralysis and Thyrotoxic Periodic Paralysis
- The prevalence of thyrotoxic PP is high in in Asian males
- Increases sodium-potassium ATPase activity on the skeletal muscle membrane is at possible cause
- Hyperinsulinaemia due to insulin resistance is also reported in thyrotoxic PP.

References

1. Thyrotoxic periodic paralysis www.uptodate.com ©2015

Patient No 114

A 29 years old female, who was grossly over-weight, lost her weight to 40 kg (BMI 13.5 kg/m^2). She resumed eating several large meals a day but developed ankle oedema, muscle weakness, hypotension (95/70 mm Hg) and drowsiness. She was admitted in a hospital for treatment. Her biochemical profile is as following:

- Serum Potassium: 2.31 mmol/L (3.5-4.5)
- Serum Phosphate: 1.65 mmol/L (1.75-1.9)
- Serum Sodium: 136 mmol/L (135-145)
- Serum Urea: 4.0 mmol/L (3.6-6.6)
- Serum Creatinine: 98 µmol/L (75-105)

a. What is most probable diagnosis?

b. Name ONE cause of hypokaleamia in this patient

Write your Answers here

Answers

Patient No 114

a. Refeeding Syndrome

b. Insulin secreted in response to oral carbohydrates cause intra-cellular shift of already deficient potassium ions

Explanation[1]

- In a patient who fast or suffers mal-nourishment due to any reason may suffer 'Refeeding Syndrome' when they are given diets rich in carbohydrates or intravenous glucose
- Insulin secretion in response to carbohydrates or glucose causes intra-cellular shift of K , Mg and P.
- These electrolyte changes may be severe enough to be fatal

References

1. Nutrition in clinical practice. The refeeding syndrome: illustrative cases and guidelines for prevention and treatment European Journal of Clinical Nutrition (2008) 62, 687–694

Patient No 115

A 68 years old male is admitted in an Intensive Care Unit with cerebrovascular accident due to sub-arachnoid haemorrhage. His investigations revealed:

- Serum Sodium 112 mmol/L (136-149)
- Serum Potassium 4.7 mmol/L (3.5-5.0)
- Urine Sodium: 74 mmol/L
- Urine Osmolality: 315 mOsmol/L
- Imaging studies of the chest: Normal

a. Write TWO most likely causes of HYPONATRAEMIA in this patient?

b. How can you differentiate the TWO conditions which may cause HYPONATRAEMIA in this patient?

Write your Answers here

Answers

Patient No 115

a. SIADH and Cerebral Salt Wasting (CSW)

b. Clear evidence of volume depletion (e.g. hypotension, decreased skin turgor, elevated hematocrit, possibly increased urea/creatinine ratio) indicates CSW

Explanation[1]

- Both conditions present with hyponatraemia
- Both can occur in cerebrovascular diseases
- SIADH is much more commonly associated with CNS disorders as compared to CSW
- CSW is probably due to impaired sympathetic release decreasing renal reabsorption of sodium and uric acid
- BNP has also been implicated as a causative factor for natriuresis

References

1. Cerebral Salt Wasting WWW.UpToDate.com 2015

Patient No 116

A 34 years old female was diagnosed as a case of Psychotic Depression and placed on an anti-depressant. She started complaining of polyuria after a few weeks of start of therapy. She underwent water deprivation test with following findings:

Six hours after Fluid Restriction:

- Serum Osmolality : 298 mOsmol/L
- Urine Osmolality: 112 mOsmol/L

Post Vasopressin

- Serum Osmolality : 292 mOsmol/L
- Urine Osmolality: 134 mOsmol/L

a. What is the most probable diagnosis in this patient?

b. Name the anti-depressant drug most likely given to the patient.

Write your Answers here

Answers

Patient No 116

a. Nephrogenic Diabetes Insipidus (NDI)

b. Lithium

Explanation[1]

- NDI is either due to resistance to ADH at collecting tubules or due to defect in the NaCl transporter in the Loop of Henle
- Mild NDI is quite common especially in elderly
- Lithium toxicity is the most common cause of NDI in adults
- In children 'Hereditary NDI' is the most common cause due to mutations in the AVPR2 gene, which encodes for a dysfunctional vasopressin V2 receptor.

References

1. Clinical manifestations and causes of nephrogenic diabetes insipidus WWW.UpToDate.com 2015

Patient No 117

A 22 years male has episodic weakness of both upper and lower limbs associated with cramps. His biochemical profile was as following

- pH: 7.49
- PCO2: 44 mmHg
- HCO3: 31 mmol/L (22-28)
- Serum Sodium 141 mmol/L (136-149
- Serum Potassium 2.7 mmol/L (3.5-5.0)
- Serum Chloride 94 mmol/L (97-106)
- Urine Spot Potassium Creatinine Ratio: 5.1 (Normal < 1.5)
- Urinary calcium (24 h) 1.21 mmol (1.25-6.0)
- Plasma active renin mass conc 135 ulu/ml (8-35)
- Plasma aldosterone 22.4 ng/dl (1-16)
- Aldosterone: Renin Ratio: 0.16

a. What is the most probable diagnosis in this patient?

b. What is the most important cause of this condition?

Write your Answers here

Answers

Patient No 117

a. Gitelman syndrome (GS)

b. Sodium and Chloride transporter defect in the distal renal tubules.

Explanation[1]

a. GS is a recessive salt-losing tubulopathy of children/young adults due to a mutation of genes encoding the human NaCl cotransporters.

b. There is a compensatory hypertrophy of JG Apparatus of the adrenals

c. Increased secretion of Renin

d. Increased Aldosterone secretion

e. Sodium levels become normal

Important Biochemical Features of GS

a. Hypokalemia

b. Metabolic alkalosis

c. Hypomagnesaemia

d. Hypocalciuria

e. Increased renin concentration (or activity)

f. Hyperaldosteronism

Genetics of GS

a. OMIM No # 263800

b. Autosomal recessive

c. Chromosome 16q13

d. Mutations affecting the **SLC12A3 gene**

e. More than 400 mutations found

f. 25% chance of siblings being affected

g. Renal thiazide sensitive sodium chloride co transporter defect

References

1. Bartter and Gitelman syndromes WWW.UpToDate.com 2015

Patient No 118

A 72 years old male, who is a known case of chronic lymphocytic leukemia for the last 10 years, was admitted in a Bone Marrow Transplant Centre for management of acute crisis. His latest lab reports showed:

- WBC count: 256 x 10^9 cells/L (3.5–10.5)
- Platelet count: 36 x 10^9 platelets/L (150–450)
- Plasma potassium

(In Lithium Heparin tube): 6.7 mmol/L (3.6–5.2)

- Serum potassium (in plain gel tube) : 4.7 mmol/L (3.6–5.2)
- No abnormalities were seen on ECG.
- Additional serum and plasma samples were sent to the Main laboratory for analysis where potassium results were 4.5 and 6.5 mmol/L, respectively.

a. What is the most probable cause of Hyperkalaemia in plasma samples

b. Write the biochemical basis of this condition

Write your Answers here

Answers

Patient No 118

a. Reverse Pseudohyperkalemia

b. Increased sensitivity of CLL cells to heparin leads to leakage of potassium from CLL cells.

Explanation[1]

- Reverse Pseudohyperkalemia is a very interesting phenomena as pseudohyperkalaemia is occurring is a “good tube” of Lithium Heparin rather than the “notorious” serum tube i.e. why it is reverse.
- Exact cause is not known but ‘increased sensitivity’ of CLL cells to heparin has been postulated.
- Lesson for the Chemical Pathologist is to repeat potassium after collection in plain tube before dishing out a report of hyperkalaemia in plasma

References

1. Reverse Pseudohyperkalaemia – Case Reports Clin Chem 2008
2. Pseudohyperkalaemia in leukaemic patients: the effect of test tube type and form of transport to the laboratory Ann Clin Biochem 2014

Patient No 119

An 18 years old female presents in A&E of a hospital with weakness in all four limbs. On examination her blood pressure was 185/105 mmHg. Her brother aged 16 years is also hypertensive. Her lab investigations were

- Na 143 mmol/L (138-145)
- K 2.9 mmol/L (3.5 - 5.0)
- Chloride 93 mmol/L (95-105)
- Bicarbonate 36 mmol/L (23_33)
- Plasma aldosterone 2.1 ng/dl (3-16)
- Active Renin Mass

Concentration (ARC): 3.8 mIU/L (8-35)

a. What is the likely diagnosis?

b. What is basic underlying defect?

Write your Answers here

Answers

Patient No 119

a. Liddle´s syndrome (or Apparent Mineralocorticoid Excess)

b. Caused by hyperactivity of the epithelial sodium channel or ameloride sensitive sodium channels (ENaC) of the cortical collecting tubule

Explanation[1]

Liddle Syndrome

- This syndrome is characterized by:
- Hypertension in young age
- Hypokalaemia
- Low renin and aldosterone
- It is a 'gain of function' mutation in the gene encoding ENaC of the collecting tubule resulting in autonomous function of these channel without the influence of aldosterone
- Can be differentiated from Primary Hyperaldosteronism by normal Na level and low aldosterone and renin

Apparent Mineralocorticoid Excess (AME)

- AME is due to deficiency in the 11betahydroxysteroid dehydrogenase enzyme type 2 isoform (11betaHSD2), which is the kidney isoform of 11betaHSD
- This enzyme is required for conversion of cortisol to cortisone.
- Excess of cortisol exerts mineralocorticoid activity
- Urinary free cortisone levels are very low or undetectable, so the ratio of cortisol to cortisone is very high.

Differentiating AME from Liddle

- AME has almost similar presenting features as Liddle i.e. Hypertension in young age, Hypokalaemia and Low renin and aldosterone

- In AME, the ratio of cortisol to cortisone in urine is 5 while it is normal in Liddle (0.3 to 0.5)
- Two other important differential diagnosis of AME can be:
    - Licorice ingestion
    - Ectopic ACTH syndrome

References

1. Genetic disorders of the collecting tubule sodium channel www.uptodate.com

Patient No 120

A 2 months old male infant presented with failure to thrive. On clinical examination, he had tachycardia and dehydration. His biochemical investigations showed:

- Plasma Glucose 4.9 mmol/L
- Serum creatinine 28 umol/L (4-29)
- Serum Sodium 124 mmol/L (136-149)
- Serum Potassium 5.9 mmol/L (3.5-5.0)
- Serum Bicarbonate 17 mmol/L (22-28)
- Serum Chloride 101 mmol/L (98-108)
- Serum Cortisol 545 nmol/L (80-580)
- Plasma Aldosterone 980 pmol/L (140-849)
- Plasma active renin mass conc 45 ulu/ml (8-35)

a. What is the most probable diagnosis?

b. Name the most probable biochemical defect

Write your Answers here

Answers

Patient No 120

a. Pseudohypoaldosteronism type 1

b. Mutations in mineralocorticoid receptor or epithelial sodium channel

Explanation[1]

- Pseudohypoaldosteronism type 1 is a rare disorder with aldosterone receptors defect
- Decreased function of Epithelial Na Channel (ENaC) is the major defect.
- It is in contrast to Liddle syndrome which is due to increased function of ENaC.
- Affected child may present with hyperkalaemia, sodium wasting, hypervolemia and metabolic acidosis.
- May be autosomal recessive or dominant varieties
- Main differentiating features from type IV RTA is raised plasma aldosterone, while type IV RTA encompasses conditions with hypoaldosteronism

(Please see table with Patient No 19 on Page 53)

References

1. Genetic disorders of the collecting tubule sodium channel www.uptodate.com

Pakistan Society of Chemical Pathologists (PSCP)

(http://www.pscp.org.pk/)

PSCP is a registered professional organization established to promote knowledge and best practices in the field of Clinical Chemistry (Chemical Pathology) in Pakistan. It is a PMDC accredited society for CME. Established in 2003, it has now nearly 200 members from all over the Pakistan. It holds annual ***scientific conferences*** and ***CME courses*** on the topics related to the fields of Chemical Pathology and Endocrinology. ***"The Spectrum"*** is its newsletter published since 2012 on yearly basis. Two ***Distance Learning Programmes (DLPs)*** have been successfully conducted by PSCP in 2013 and 2014 and ***Structured Assessment of Skills (SAS)*** was conducted in 2015 to impart knowledge and skills in the field of Chemical Pathology. During this course 10 patient records were sent to the teachers of Chemical Pathology to conduct QADIS (Quick Assessment of Data Interpretation Skills) and a practical examination. This activity was conducted on monthly basis for one year. All these cases have been carefully sorted out and arranged according to the organ system of the human body.

So this **'QADIS Book'** is a compilation of 120 patient records. Each record comprises clinical information and biochemical data, followed by correct diagnosis and a brief description of the condition. At least one reference has been provided at the end of each patient record. It has been designed in such a way that both undergraduate and postgraduate students can carry out a self-directed learning activity by writing the answers on the book, and use it as a workbook as well as source of knowledge of disease pathophysiology. These cases are also available as PowerPoint Presentations for the teachers alongwith the related articles. This book surely represents academic enthusiasm of all the teachers of Chemical Pathology in Pakistan.