JUST ANOTHER DAY IN CLINICAL CHEMISTRY

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1

OBJECTIVES

- Evaluate interesting cases that are observed in the clinical chemistry department.
- Correlate lab results and patient history with a presumptive diagnosis.
- Assess the necessity for confirmatory testing for patient diagnosis.

2

CASE 1: HYPOCALCEMIA IN A NEONATE

3

PRESENTATION

25-day old male

ER with choking and rapid breathing post-feeding

History: Systolic murmur

4

- Infant was admitted
- Treated for aspiration pneumonia
  - Penicillin & gentamycin
- Echocardiogram:
  - Perimembranous ventricular septal defect (VSD) in failure

5

DAY 6

Developed seizures

- Bilateral upper limb and left lower limb jerky movements
- Twitching of eyelids and lips
- Each episode lasted 30 sec – 1 min

Stable vital signs

No obvious facial anomalies

Unremarkable neurological exam

6

Test	Day 6 (after seizure)	Reference Interval
Urea (mg/dL)	28.52	19.22-48.65
Sodium (mmol/L)	133	136-145
Potassium (mmol/L)	4.47	3.5-4.5
Creatinine (mg/dL)	0.53	0.31-0.87
Total protein (g/dL)	5.1	6.4-8.3
Albumin (g/dL)	3.5	3.8-5.4
ALP (U/L)	410	<449
Adjusted Calcium(mg/dL)	5.64	9.0-11.0
Magnesium (mmol/L)	1.7	1.51-2.21
Phosphate (mg/dL)	13.84	3.87-6.97
Glucose (mg/dL)	84.1	50.0-79.9
Ammonia (µg/dL)	55.41	22.41-84.05
Lactate (mmol/L)	0.92	0.5-2.2

Test	Day 6 (after seizure)	Reference Interval
PTH (pg/mL)	21.41	14.90-56.86
25(OH)D (ng/mL)	21.2 (Day 7)	24-64
Venous Blood Gas:		
pH	7.395	7.34-7.45
p02 (mmHg)	36.8	70-85
pCO2 (mmHg)	60.8	27-43
Bicarbonate (mmol/L)	33.5	19-25
Random urine calcium (mmol/L)	4.61	6.8-21.24
Random urine creatinine (mg/dL)	6.78	39.14-259.04
Random urine phosphate (mg/dL)	5.30	40.3-136.4
Urine calcium:creatinine ratio (mmol/L)	1.9	<1.5

7

WHAT DO RESULTS INDICATE AT THIS POINT?

- Hyponatremia → caused by decreased plasma volume in heart failure
  - Leads to secondary aldosteronism
- Hypoproteinemia & hypoalbuminemia → attributed to malnutrition, hemodilution from the fluid overload in heart failure, and increased intravascular permeability

8

WHAT DO RESULTS INDICATE AT THIS POINT?

- Venous blood gas:
  - Hypoxia, hypercapnia, high bicarbonate, normal pH
  - Mixed acid-base disorder
    - Metabolic alkalosis → due to HF
    - Underlying respiratory acidosis

9

WHAT DO RESULTS INDICATE AT THIS POINT?

- Normal PTH
- Increased urine calcium:creatinine ratio
- Hypophosphaturia
- Hypocalcemia

Hypoparathyroidism

- Vitamin D deficient

10

MANAGEMENT

Patient given IV calcium gluconate

Followed by oral calcium carbonate (100mg; 4x/day)

Day 7 → serum calcium: 6.53 mg/dL; serum phosphate: 12.28 mg/dL

Day 8 → Serum calcium: 8.50 mg/dL; serum phosphate: 8.71 mg/dL

Discharge: Serum calcium: 9.18 mg/dL; serum phosphate: 7.84 mg/dL

No thymus visible on chest x-ray

11

FURTHER DISCUSSION

Common causes of neonatal seizures:

- Hypoxic ischemic encephalopathy
- Intracranial hemorrhage
- Intracranial infections
- Metabolic and electrolyte disorders
- Cranial nervous system malformations
- Inborn errors of metabolism
- Epileptic syndromes

Hypocalcemia

12

FURTHER DISCUSSION

Causes of neonatal hypocalcemia:

- **Early-onset:**
  - Occurs in first 72 hours of life
  - Prematurity
  - Asphyxia
  - Preeclampsia
  - Sepsis
- **Late-onset:**
  - Occur after 72 hours
  - Increased phosphate load
  - Hypomagnesemia
  - Vitamin D deficiency
  - Hypoparathyroidism

13

ANOTHER LOOK AT INITIAL LAB RESULTS:

Test	Day 6 (after seizure)	Reference Interval
PTH (pg/mL)	21.41	14.90-56.86
25(OH)D (ng/mL)	21.2 (Day 7)	24-64
Creatinine (mg/dL)	0.53	0.31-0.87
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Urine calcium:creatinine ratio (mmol/L)	1.9	<1.5

14

DIAGNOSIS

- Hypocalcemia secondary to hypoparathyroidism
- Perimembraneous VSD
- Possible absence of thymus
- 22q11 deletion syndrome

15

BETTER KNOWN AS…

DiGeorge Syndrome

16

- Diagnosis confirmed with FISH → deletion in chromosome 22
- Ultrasonography → presence of thymus
- Patient did not have typical facial features of DiGeorge Syndrome

17

DIGEORGE SYNDROME

- Commonly associated with congenital hypoparathyroidism
- Characterized by absence or underdevelopment of thymus
  - Low T cell counts
  - Increased susceptibility to infection
- Chromosome 22q11.2 deletions may be a random occurrence or an autosomal dominant trait
  - Confirm deletion with FISH

18

DIGEORGE SYNDROME

- Manifestations of 22q11.2DS vary & often involve multiple organs
  - Congenital heart disease
  - Spinal, renal, and/or skeletal anomalies
  - Speech/language impairment
  - Thyroid and immune disorders
- Some manifestations are not obvious in neonates → further evaluations throughout life

19

PATIENT DISCHARGED

- Managed by multidisciplinary team
- Scheduled for further evaluation of kidney involvement, hearing assessment, continuation of treatment, monitoring calcium, magnesium, & phosphate
- Follow-up with pediatric endocrinologist, cardiologist, & genetics clinic

20

CASE 2: PRESENTATION OF HYPERGLYCEMIA IN AN ELDERLY PATIENT

21

PRESENTATION

66-year-old female

History of hypertension, fatty liver, & prediabetes

Comes to ER with dyspnea, abdominal pain, weakness

22

PATIENT HISTORY:

- Diarrhea & vomiting over past few months
  - Increased in frequency over last 3 days
- Accompanied by worsening abdominal pain
- Polyuria and polydipsia over previous 3 weeks

23

Test	Result	Reference interval
Glucose (mg/dL)	>1450	70-140
Sodium (mmol/L)	101 (corrected 124)	135-145
Potassium (mmol/L)	3.2	3.6-5.2
Bicarbonate (mmol/L)	20	22-29
Calcium (mg/dL)	10.6	8.8-10.2
BUN (mg/dL)	32.4	6.0-21.0
B-hydroxybutyrate (mmol/L)	2.6	<0.4
Troponin (ng/L)	32	≤10
NT-Pro BNP (pg/mL)	2857	≤193
Creatinine (mg/dL)	1.83	0.59-1.04
Hemoglobin A1C (%)	13	4.2-5.6
Lipase (U/L)	269	13-60

Test	Result	Reference interval
Calculated osmolality (mOsm/kg)	340	275-295
Arterial blood gas		
pH	7.36	7.35-7.45
pCO_2 (mmHg)	35.5	35-45
CBC		
Hemoglobin (g/dL)	14.9	11.6-15
Hematocrit (%)	46.2	35.5-44.9
RBC ($x10^{12}$/L)	5.34	3.92-5.13
MCV (fL)	86.5	78.2-97.9
Platelets ($x10^9$/L)	318	175-371
WBC ($x10^9$/L)	18.3	3.4-9.6
Neutrophils ($x10^9$/L)	16.2	1.56-6.45
Lymphocytes ($x10^9$/L)	0.52	0.95-3.07

24

INITIAL MANAGEMENT

- 1 L bolus 0.9% sodium chloride
- 10 U subcutaneous insulin aspart
- 8 doses of 10mEq potassium chloride
- Continuous IV insulin (1.556-7.78 U/h)
- 1 L continuous PLASMA-LYTE A

25

- Admitted to ICU
- Quickly decompensated
- Agitated & Disoriented
- Hypotensive
- Tachypneic
- Required intubation & sedation

26

FURTHER TESTING

MRI	No evidence of cerebral edema or structural changes
Chest x-ray	Observed infiltrates
BAL	*Enterobacter cloacae* *Candida albicans* *Aspergillus*
Plasma lactate	8 mmol/L (RR: 0.6-2.3 mmol/L)

27

DIAGNOSIS

- Extreme hyperglycemia
- Hyperosmolarity
- Severe dehydration
- Neurologic impairment

Hyperosmolar hyperglycemic state (HHS)

28

DIFFERENTIAL DIAGNOSIS

HHS

- Hyperglycemia & hyperosmolarity
- Dehydration
- Neurologic impairment
- **Usually associated with T2DM**
- **Slow progression**
- **Insulin resistance**

DKA

- Hyperglycemia & hyperosmolarity
- Dehydration
- Neurologic impairment
- **Increased ketones**
- **Metabolic acidosis**
- **Usually associated with T1DM**
- **Rapid onset**
- **Insulin deficiency**

29

HHS

- Initial symptoms: polyuria & polydipsia
- Delayed diagnosis is common
- Usually diagnosed after development of dehydration
- Dry mucus membranes, decreased skin turgor, hypotension, weakness, altered mental status
- Abdominal distension

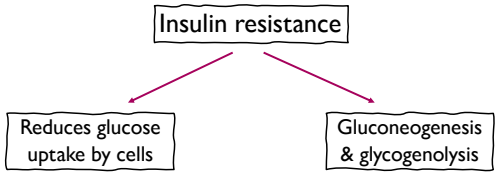
30

EPIDEMIOLOGY

- Who is most likely to develop HHS?
  - Elderly with type 2 diabetes
- Infections develop in 40-60% of cases
  - Gram-negative pneumonia
  - UTI
  - Sepsis
- Mortality rate: 10-50%
- Precipitating factors:
  - Undiagnosed diabetes
  - Pancreatitis
  - Heart attack
  - Stroke
  - Trauma
- Hospitalization for HHS account for <1% of diabetes-associated admissions

31

PATHOPHYSIOLOGY



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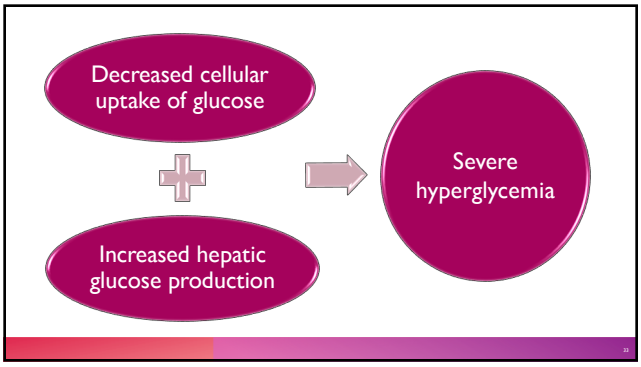

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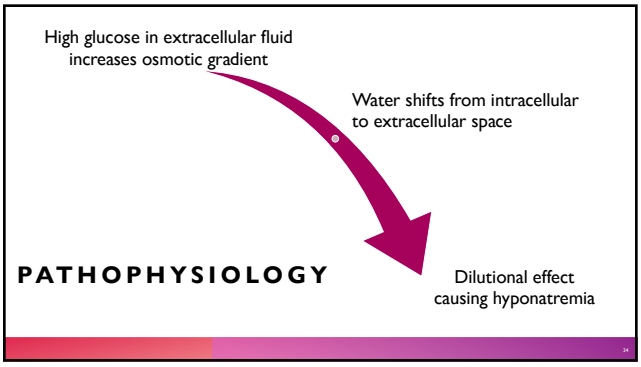
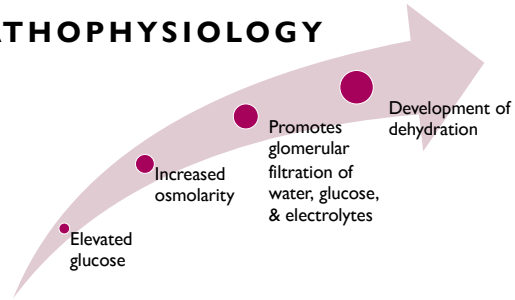


34

PATHOPHYSIOLOGY



35

EFFECTS OF HHS

Multi-system impairment

36

DIAGNOSTIC CRITERIA FOR HHS

- Glucose >600 mg/dL
- Plasma osmolality >320 mOsm/kg
- pH >7.30
- Elevated BUN & creatinine
- Elevated WBC
- Increased hematocrit

37

TREATMENT FOR PATIENT

- Hemoglobin A1C → verified poor glycemic control over preceding months
- Plasma glucose & dehydration worsened from consumption of glucose-rich beverages
- Elevated BUN & creatinine → renal impairment
- Bacterial pneumonia
- Following extensive hospitalization → patient discharged to long-term care facility

38

CASE 3: AN UNUSUAL CASE OF HYPOKALEMIA

39

PRESENTATION

- 47-year-old male
- 6-year history of hypertension
- Referral from detention center with weakness & hypokalemia
- Previous facility treated critically low potassium with IV and oral potassium

40

CURRENT FINDINGS:

- Normally developed male
- No remarkable history
- No clinical signs of malnutrition
- No diarrhea, vomiting, laxative abuse, intestinal obstruction or infection, or diuretic use
- BP was 144/81 mmHg while on antihypertensives

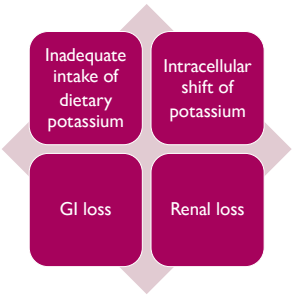
41

Test	Result	Reference interval
Sodium (mmol/L)	142	136-145
Potassium (mmol/L)	4.8	3.5-5.1
Chloride (mmol/L)	104	98-107
Bicarbonate (mmol/L)	21	22-29
Anion gap (mmol/L)	17	7-15
BUN (mg/dL)	19	6-20
Creatinine (mg/dL)	1.46	0.67-1.17
eGFR (mL/min)	52	>60
Glucose (mg/dL)	123	70-99
Calcium (mg/dL)	10.6	8.5-10.6
Phosphorus (mg/dL)	3.9	2.7-4.5
Aldosterone (ng/dL)	32	0.0-30.0
Renin activity (ng/mL/hr)	<0.2	0.5-4.0

- Normal thyroid function tests
- Normal serum cortisol
- Abdominal CT revealed right adrenal mass measuring 2.2 cm

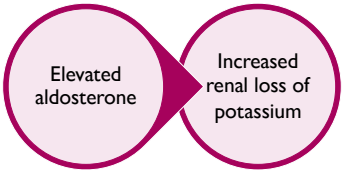
42

CAUSES OF HYPOKALEMIA



43

WHY DOES THIS PATIENT HAVE HYPOKALEMIA?



44

Primary hyperaldosteronism
- Excess production of aldosterone by adrenal gland
- Low plasma renin concentration

Secondary hyperaldosteronism
- Increased aldosterone due to excessive renin secretion
- High plasma renin concentration

45

PRIMARY HYPERALDOSTERONISM

Prevalence at 5-15%

Caused by:
- Bilateral adrenal hyperplasia (~65%)
- Unilateral aldosterone-producing adenoma (~30%)
- Adrenal carcinoma, familial hyperaldosteronism, idiopathic hyperaldosteronism

Classic signs:
- Hypertension
- Hypokalemia
- Metabolic alkalosis

46

SECONDARY HYPERALDOSTERONISM

Caused by:
- Diuretics
- Renovascular disease
- Renin secreting tumor (rare)

Occasional observed in patients with:
- Cirrhosis
- Nephrotic syndrome
- Heart failure

47

DIAGNOSIS OF PRIMARY HYPERALDOSTERONISM

- Initial screening test:
  - Aldosterone/renin ratio (ARR)
  - Renin is suppressed (<1 ng/mL/hr) and aldosterone is inappropriately high (>15 ng/dL) → PA
- If screening test indicates probable PA → perform aldosterone suppression test
- Following diagnosis → perform adrenal CT → distinguishes BAH versus unilateral APA

48

CASE RESOLUTION

- Patient had increased aldosterone with undetectable renin activity
- ARR was greatly increased

Primary hyperaldosteronism

- Adrenal vein sampling (AVS) demonstrated good positioning of sampling catheters in adrenal veins
  - Confirmed presence of unilateral APA

49

FURTHER DISCUSSION

Laparoscopic right adrenalectomy perform 13 weeks after confirmation of APA

Resected gland contained bright yellow-orange sold mass

Pathology confirmed cortical adenoma

50

PATIENT OUTCOME

- Following surgery:
  - Patient became hypertensive (systolic BP at 190-200 mmHg)
  - Developed ST depression → indicates possible myocardial ischemia
- Troponin T: normal
- Treated hypertension with hydralazine
- Next day:
  - BP normal without medication
  - Normal ECG
- Patient discharged

51

CASE 4: GI SYMPTOMS & SHOCK IN PEDIATRIC PATIENT (PARIS, FRANCE)

52

PRESENTATION

7-year-old Congolese male

ER with rash, abdominal pain, vomiting, diarrhea,

5 days of fever

No relevant family or personal history

NOTE: This took place spring 2020, during national lockdown due to pandemic

53

PHYSICAL EXAM

Abdominal CT: moderate peritoneal effusion, gall bladder hydrops, basal lung opacities suggestive of COVID-19

Acute abdomen

Cervical lymphadenopathy

Neck stiffness

54

Test	Result	Reference interval
WBC ($x10^9$/L)	5.1	5.5-11.5
Neutrophils ($x10^9$/L)	9.6	1.1-8.0
Lymphocytes ($x10^9$/L)	0.3	1.5-6.5
Hemoglobin (g/dL)	5.3	11.5-13.5
Platelets ($x10^9$/L)	108	175-420
CRP (mg/L)	160	<6.0
Procalcitonin (µg/L)	31	<0.5
IL-1 B (pg/mL)	5.8	<15
IL-6 (pg/mL)	162	<8.5
TNF-α (pg.mL)	75	<20
D-dimers (µg/L)	5653	<500
Fibrinogen (mg/dL)	470	150-350
Prothrombin time (%)	48	>70

Test	Result	Reference interval
Albumin (g/L)	16	35-50
Sodium (mmol/L)	126	136-146
Potassium (mmol/L)	2.6	3.1-4.7
Creatinine (mg/dL)	0.45	0.34-0.54
AST (U/L)	92	9-45
ALT (U/L)	37	7-40
GGT (U/L)	72	5-25
LD (U/L)	446	125-243
Bilirubin, total (mg/dL)	0.35	<1.0
Lipase (U/L)	527	7-60
Lactate (mg/dL)	33.3	4.0-15.8

55

ADDITIONAL LAB TESTS

- CSF: normal findings
- COVID-19 RT PCR from NP swab: Positive

56

AFTER ADMISSION

- Signs of shock
- Tachycardia (heart rate 140 bpm)
- Hypotension (62/37 mmHg)
- Septic shock? Toxic shock?
  - Started on broad spectrum antibiotics
- Blood & urine cultures: No growth

Patient transferred to PICU

57

- ECG: indicated pericarditis and myocarditis with posterolateral hypokinesia and reduced left ventricular ejection fraction

Test	Result	Reference interval
CK (U/L)	561	30-180
hs-TnI (ng/L)	447	<26
BNP (ng/L)	6503	<100

- Received vasoactive and inotropic agents
- Patient put on ventilator

58

- Patient developed:
  - Strawberry tongue
  - Erythema
  - Cracking lips
  - Bilateral conjunctivitis
- Patient treated with IV immunoglobulins (IVIG)

Could this be Kawasaki disease?

59

FURTHER TESTS

- Anti-SARS-CoV-2 IgG: Positive
- Nasopharyngeal RT-PCR for SARS-CoV-2: Negative (Days 5 & 8)
- NP testing for other viruses: Negative

- Questioned mother:
  - Patient had no recent history of viral illness
  - Mom experienced symptoms consistent with COVID-19 about 40 days prior to child's fever

60

3 DAYS LATER…

- Patient showed signs of improvement
- Normal body temperature
- Resolution of clinical signs
- LEVF normalized
- TnI and CRP rapidly decreased

61

DIAGNOSIS:

Kawasaki Disease-like multisystem inflammatory syndrome

This is one of the earliest cases of KD-like illness related to SARS-CoV-2

62

KAWASAKI DISEASE

- Multisystem vasculitis
- Primarily affects children under 5
- Affects 25/100,000 in Western countries
- 25% develop coronary artery aneurism

63

DIAGNOSTIC CRITERIA:

Fever lasting >4 days

AND

4 out of 5 of the following signs/symptoms:

- Oral changes
- Cervical lymphadenopathy
- Bilateral conjunctivitis without exudate
- Polymorphous exanthema
- Extremity changes

64

If all criteria is not met → diagnosis of "Incomplete KD"

Based on presence of clinical, laboratory, and ECG findings

65

DIFFERENTIAL DIAGNOSIS

- Bacterial sepsis
- Toxic shock syndrome
- Cardiogenic shock secondary to viral myocarditis

- These diagnoses ruled out following negative bacterial cultures and rapid decline in CRP and TnI following IVIG

66

KD SHOCK SYNDROME (KDSS)

- Uncommon, yet severe complication of Kawasaki disease
- Affects 1.5-7% patients with KD
- Higher inflammatory markers, frequent coronary abnormalities, GI symptoms, higher D-dimer
- More severe anemia, hypoalbuminemia, hyponatremia, hypokalemia

67

OBSERVATION DURING COVID-19 PANDEMIC:

- Cases of severe KD-like illness in children an adolescents
  - Shock
  - Myocarditis
  - History of recent SARS-CoV-2 infection
- KD-like illness related to SARS-CoV-2

This was something new!

Hyperinflammatory syndrome with multiorgan involvement

68

- "Multisystem inflammatory syndrome in children" (MISC) in U.S.
- "Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection" (PIMS-TS) in Europe

69

MIS-S & PIMS-TS

- Patients are older
- Often from Sub-Saharan African decent
- Commonly experience
  - GI involvement
  - Shock
  - Myocarditis
  - Profound lymphopenia

This patients fits this description of this KD-like illness

70

MORE ABOUT KD-LIKE ILLNESS

- Gall bladder hydrops
- Abnormal liver enzymes
- Pancreatitis
- Hypoalbuminemia
- Lymphopenia

71

FURTHER DISCUSSION ABOUT THE PATIENT

- Troponin I and BNP elevated
  - Decreased soon after IVIG

Indicates myocarditis due to inflammation as opposed to ischemia or necrosis

- Cardiac biomarkers are relevant → predictors of coronary arty lesions in KD

72

FURTHER DISCUSSION ABOUT THE PATIENT

- In adults → COVID-19 responsible for cytokine storm
- Shock likely due to elevated inflammatory markers
  - Appeared to be post-viral immunological reaction
- Rapid resolution of all abnormalities following IVIG treatment → supports diagnosis of KD-like multisystem acute vasculitis in this patient

73

PATIENT DISCHARGED

- 8-day hospitalization
- Follow-up labs one week after discharge:
  - CRP decreased (160 mg/dL → 8.5 mg/L → <0.5 mg/L)
  - Procalcitonin decreased (31 µg/L → 1.0 µg/L → 0.04 µg/L)
  - TnI decreased (447 ng/L → 62 ng/L → 19 ng/L)
- One month after discharge:
  - ECG & MRI → normal coronary arteries and cardiac function

74

IN CONCLUSION…

- As laboratory professionals, we play a vital role in patient care
- We are an integral part of the health care team
- Our knowledge and expertise is priceless!

- Always keep your eye out for those interesting cases…they keep us on our toes!

75

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76