Neuropsychiatric Manifestations of Neuroendocrine Tumors

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Disclosures

• I have no conflicts of interest to disclose
Learning Objectives

• Recognize diversity of neuropsychiatric syndromes and symptoms associated with various neuroendocrine tumors

• Understand variability of timing of neuropsychiatric symptom onset

• Identify symptoms that might indicate utility of further neuropsychiatric evaluation
Case 1

Patient Characteristics
• 59 year-old woman
  • Psychiatric history of bipolar disorder type II
  • Medical history of gastric bypass and complications (SBO, adhesions)
  • Initial presentation for enterococcal bacteremia and for episodic confusion
  • Malnutrition noted on admission and treated throughout hospitalization with various forms of feeding

Initial Endocrine Findings
• Fingerstick glucose minutes after completion of D10 infusion: 50, 44, 39, and 18 mg/dL
  • No observed symptoms
  • Venous glucose: 69 mg/dL
  • Fingertips cyanotic and cool
• Initial assessment: impaired microcirculation = low capillary glucose, preserved systemic (pseudohypoglycemia)
Case 1

Clinical Course

• Episode of somnolence and difficulty with arousal associated with discontinuation of tube feeds the day prior
  • Capillary glucose: 53 mg/dL
  • Venous glucose: 57 mg/dL
  • Dextrose → Alert, oriented, and appropriate

• Later that day: episode of agitation with confusion, restlessness, memory difficulties, and speaking nonsensically and pressured
  • Improved over several hours with D5 running

• Later still: another episode of agitation treated with quetiapine
  • Somnolence 3 hours later, glucose 46 mg/dL from PICC
  • Incomplete improvement with D50
  • Psychiatry consulted due to altered mental status attributed to quetiapine

• Multiple recurrent episodes of confusion, near unresponsiveness, intermixed with returns essentially to baseline: possible delirium?
  • Psychiatry: atypical delirium, recommend EEG and further evaluation of recurrent hypoglycemia
Case 1

Further Workup

- Insulin studies ten minutes prior to a capillary glucose value of 60 mg/dL:
  - Insulin: 5.7 mcIU/mL (ref: 2.6-24.9)
  - C-Peptide: 4.5 ng/mL (ref: 1.1-4.4)
  - Proinsulin: 35 pmol/L (ref: 3-20)

- EEG: Mild diffuse slowing of the background and frontal intermittent rhythmic delta activity

- Diagnosis: Unfortunately unknown at this point, but high suspicion for insulinoma in addition to pseudohypoglycemia
Insulinoma: Episodic Confusional State

Neuroglycopenic Symptoms

<table>
<thead>
<tr>
<th>Main presentation</th>
<th>Duration of patient history</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>&lt;1 year</td>
<td>1-5 years</td>
<td>&gt;5 years</td>
</tr>
<tr>
<td>Patient number</td>
<td>25</td>
<td>9</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Confusion</td>
<td>18 (72)</td>
<td>7 (77.8)</td>
<td>6 (54.5)</td>
<td>5 (100)</td>
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<tr>
<td>Weakness</td>
<td>17 (68)</td>
<td>8 (88.9)</td>
<td>7 (63.6)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (64)</td>
<td>7 (77.8)</td>
<td>7 (63.6)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Fainting</td>
<td>15 (60)</td>
<td>4 (44.5)</td>
<td>9 (81.8)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>12 (48)</td>
<td>6 (66.7)</td>
<td>3 (27.3)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Slow reaction</td>
<td>12 (48)</td>
<td>4 (44.5)</td>
<td>6 (54.5)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Memory disorder</td>
<td>10 (40)</td>
<td>2 (22.3)</td>
<td>6 (54.5)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Gaitism</td>
<td>6 (24)</td>
<td>1 (11.1)</td>
<td>3 (27.3)</td>
<td>2 (40)</td>
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<tr>
<td>Abnormal behavior</td>
<td>5 (20)</td>
<td>2 (22.3)</td>
<td>2 (18.2)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>4 (16)</td>
<td>0</td>
<td>1 (9.1)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Coma</td>
<td>2 (8)</td>
<td>0</td>
<td>1 (9.1)</td>
<td>1 (20)</td>
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<tr>
<td>Hysteria</td>
<td>2 (8)</td>
<td>1 (11.1)</td>
<td>1 (9.1)</td>
<td>0</td>
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<tr>
<td>Sleepiness</td>
<td>2 (8)</td>
<td>1 (11.1)</td>
<td>1 (9.1)</td>
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<tr>
<td>Personality change</td>
<td>2 (8)</td>
<td>1 (11.1)</td>
<td>1 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Barylalia</td>
<td>2 (8)</td>
<td>0</td>
<td>1 (9.1)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate percentages.

Why do neuropsychiatric symptoms matter?

Figure and table from Ding et al., 2010.

Fig. 1. Distribution of rate of insulinoma misdiagnosis. The rate of PNS is higher than that of PNNS.
Case 2

Patient Characteristics

- 47 year-old woman
  - Psychiatric history of bipolar disorder
  - Medical history of seronegative systemic lupus erythematosus (SLE)
  - Both diagnoses ~7 years prior

- Several months of abdominal pain, weight loss, anorexia, and intermittent skin rash
  - Remote history of: erythematous, scaling rash on face and groin; ulcerative eruption of mucous membranes; spontaneous late-term abortions; and kidney injury

- Psychiatric consulting service asked to evaluate patient for management of bipolar disorder

Psychiatric Exam

- Tearful, withdrawn, decreased energy and concentration, excessive guilt, poor appetite, and poor sleep
  - No suicidality or psychosis
  - Clear discrete periods of expansive mood and depression, but no mania

- Multiple failed trials of antidepressants and mood stabilizers
  - Also limited benefit from treatments targeting SLE

Case adapted from McGenva et al. 2009
Case 2

Medical Evaluation and Outcome

- Glucagon level 1150 pg/mL (ref: 50-200)

- Radiologic and histologic studies confirmed glucagonoma

- Treatment with distal pancreatectomy and splenectomy plus octreotide

- Rapid improvement in depressive symptoms and SLE-like symptoms following tumor excision

Case adapted from McGenna et al. 2009
Glucagonoma: Glucagonoma Syndrome

**Characteristic Symptoms**
- Anorexia
- Necrolytic migratory erythema (see photo)
- Diabetes
- Anemia
- Venous thrombosis
- Nonspecific symptoms (GI symptoms, abdominal pain, ulcers)
- Neuropsychiatric

**Neuropsychiatric Symptoms**
- Depression
  - Sleep, interest/pleasure, guilt, energy, concentration, appetite, psychomotor, suicidality
- Psychosis
- Dementia
- Insomnia
- Ataxia
- Proximal muscle weakness
- Optic atrophy

McGerva et al. 2009
Glucagonoma Syndrome: Key Points

• Intermittent symptoms are common with NETs

• Identification of syndromes is important

• Prior diagnoses may be inaccurate
  • Consider treatment failures

• Narrow focus can lead to compartmentalization of symptoms (psychiatric, endocrine, dermatologic, etc.)
Case 3

**Patient Characteristics**

- 56 year-old woman
  - No psychiatric history prior to 6th decade
  - Medical history of hypertension and impaired fasting glucose – unknown onset

- Admitted to psychiatry for 6 week episode of sleep-deprived energy enhancement, grandiosity, flight of ideas, pressured speech, disorganization, distractibility, hypersexuality, and agitation
  - Diagnosis: Bipolar disorder type I, Manic

Case 4

**Patient Characteristics**

- 61-year-old woman
  - 18-year history of bipolar disorder, type I, 5 prior manic episodes, last episode 12 years prior

- 10-day change in behavior with manic symptoms plus paranoid delusions qualitatively different from any prior psychotic symptoms
  - Diagnosis: Bipolar disorder type I, Manic
Case 3

Initial Treatment and Recurrence

- Partial response noted with antipsychotics and mood stabilizers
- ~2 years later, discontinuation of medications → recurrent psychotic manic episode
- Critically low serum potassium of 1.9 mmol/L (ref: 3.5-5.1) with hypertension and hyperglycemia
  - Hospitalized on a medical floor

Case 4

Initial Evaluation and Treatment

- Hypokalemia, 1.6 mmol/L (ref: 3.5-5.1)
- Hyperglycemia, 141 mg/dL (ref: 70-100)
- Treatment: potassium replacement; clonazepam; olanzapine; lithium carbonate → euthymia and resolution of psychosis by day 7
Case 3

**Endocrine Findings**
- AM Cortisol: 54 and 61 mcg/dL (ref: 7-25)
- ACTH: 189 pg/mL (ref: 10-60)
- Urinary free cortisol: 3953 mcg/24 hrs (ref: 3.5-45)
- Inferior petrosal sinus sampling → ectopic ACTH

**Imaging and Surgical Findings**
- Nodule in right middle lobe of lung with abnormal uptake
- Surgical removal successful
  - Pathology: pulmonary carcinoid with ACTH production

Case 4

**Endocrine Findings**
- AM Cortisol: 142 mcg/dL (ref: 7-25)
- ACTH: 939 pg/mL (ref: 10-60)
- Urinary free cortisol: 3018 mcg/24h (ref: 3.5-45)

**Imaging and Surgical Findings**
- Imaging/pathology: liver, lung, bone, and brain masses → metastatic small cell carcinoma
Case 3

Outcome
• Complete resolution of endocrine lab abnormalities and mood symptoms
  • Return to psychiatric baseline within weeks
• Off psychiatric meds over 24 months with no recurrence of psychiatric symptoms

Case 4

Short-Term Outcome
• Palliative chemotherapy → resolution of endocrine lab abnormalities
• Lithium, olanzapine and clonazepam continued with no recurrence of psychiatric symptoms
  • Improvement in quality of life noted

Long-Term Outcome
• Patient died from brain metastases eleven months later
Pulmonary Carcinoid and Small Cell Lung Cancer: Ectopic ACTH Syndrome

**Key Points**

• Physical symptoms but may be late or absent

• Most common neuropsychiatric symptoms: insomnia, irritability, depression, anxiety, sexual changes
  • Mania, psychosis much less common but possible

• Neuropsychiatric features more severe than other forms of Cushing’s Syndrome
  • Perhaps due to combined effects of ACTH + cortisol

• Symptoms resolve with tumor/endocrine treatment (70-80% of cases)
  • Resolution can take months
  • Depressive symptoms and cognitive symptoms may persist

Case 5

Patient Characteristics
- 56 year-old woman
  - Psychiatric history of post-partum psychosis
  - Medical history of small cell lung carcinoma
- Admitted to medical oncology inpatient service for psychosis with immediate psychiatric consultation

Pertinent Historical Information
- Left-sided weakness 20 days prior to admission
  - MRI $\rightarrow$ right frontal metastasis with edema
  - Dexamethasone 4 mg twice per day
- 10 days prior to admission, patient speaking to God and not sleeping
  - Dexamethasone 1 mg twice per day $\rightarrow$ symptom resolution
- 8 days prior to admission, symptom recurrence with “agitation”
  - Quetiapine + benzo at bedtime $\rightarrow$ mild improvement
- Day of admission: presented for gamma knife therapy
  - Disorganized, hyperreligious
Case 5: Imaging Findings

**Left:** 1.7 cm AP x 1.5 cm TV x 2.1 cm SI mass at the grey-white junction of the paramedian right superior frontal gyrus extending to pial surface

**Right:** Surrounding vasogenic edema throughout the centrum semiovale
Case 5

Psychiatric Examination
• Hypersexual, no concern for modesty
• Speech nonsensical and unrelated
• Odd concerns about pregnancy
• Hallucinating
• Markedly impaired attention concentration

Assessment, Treatment, and Outcome
• Hyperkinetic delirium due to steroids, metastatic mass, and edema
  • Steroids discontinued
  • Antipsychotics for psychotic symptoms and sleep
• Over 24 hours, resolution of psychosis
  • Able to consent to gamma knife therapy
• Gamma knife successful
  • No recurrence of symptoms at post-radiation day 6
  • Haloperidol (low-dose) continued
Metastatic Disease: Mass Effects

**Mass Effects and Location Associations**
- Mood symptoms (depression or mania) – frontal
- Psychosis – pituitary, frontal, temporal
- Memory problems – thalamic, temporal
- Personality changes – frontal
- Anxiety – nonlocalized
- Anorexia – hypothalamic
- Seizures – temporal
- Psychiatric symptoms can be alone in up to 18% of cases
  - “Nonfocal” neurological exam

**Clues to Consider Neuroimaging**
- New-onset psychosis
- New-onset mood symptoms in patient with known primary
- New-onset personality changes
- Neuropsychiatric symptoms later in life

Madhusoodanan, et al. 2010
Madhusoodanan, et al. 2015
Other Neuropsychiatric Manifestations of Neuroendocrine Tumors

- Carcinoid syndrome
  - Mood symptoms (depression/mania/hypomania): up to 50%
  - Anxiety: up to 35%
  - Confusion: up to 35%
  - Insomnia
  - Irritability, aggression, and poor impulse control

- Diminished brain serotonin levels seemingly due to depletion of systemic tryptophan

The man was addicted to moaning,
Confusion, edema and groaning,
Intestinal rushes,
Great tri-colored blushes
And died from too much serotonin

Much peripheral serotonin production,
Can lead to a striking induction
Of depressive affects,
Sleeping defects
And abnormal mental perceptions

Poem: Bean and Funks, 1963 (first verse); Major et al., 1973 (second verse);
Russo et al., 2004
Other Neuropsychiatric Manifestations of Neuroendocrine Tumors

- Neurologic paraneoplastic syndromes
  - Lambert-Eaton myasthenic syndrome: proximal muscle weakness
    - SCLC and atypical carcinoids
    - Antibodies against P/Q type calcium channels
  - Paraneoplastic cerebellar degeneration: ataxia, dysarthria, nystagmus, etc.
    - SCLC, gastric carcinoid?
    - Antibodies against purkinje cells
  - Limbic encephalitis: personality changes, irritability, memory loss, seizures, dementia, catatonia
    - Often predates tumor diagnosis
    - SCLC, thymic carcinoid, non-NETs
    - Anti-Hu, anti-Ma, anti-NMDA

Kaltsas et al., 2010
Recognition of Neuropsychiatric Symptoms

• Use your own intuition

• Ask the patient:
  • “Are you depressed?”
  • “Do you still find enjoyment in things you used to enjoy?”

• Feel comfortable referring to psychiatry

• Adequately treated psychiatric symptoms = improved quality of life
  • Depression has particularly high morbidity

Kroenke, Spitzer, and Williams 2003
Final Thoughts

• Neuropsychiatric symptoms can arise at any point during the diagnostic and treatment process for neuroendocrine tumors, including before a tumor is ever suspected or identified

• Have a high index of suspicion for medical causes of new-onset psychiatric illnesses later in life

• Treatment of the neuropsychiatric manifestations of neuroendocrine tumors is most frequently accomplished by treatment of the tumor itself, so psychiatric intervention needs to occur in parallel (not in series) with medical/surgical interventions

• Try to prevent diagnosis bias – our propensity to label people, ideas, or things based on our initial opinions of them and our inability to reconsider those judgments once we have made them
Thank you!

Questions & Discussion