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**THE DIFFERENTIAL DIAGNOSIS OF CONGENITAL DISORDERS THAT INCLUDE PSYCHOSIS**

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**BACKGROUND:** Neuropsychiatrists are often called upon to evaluate psychotic individuals for possible neurological or neurodevelopmental etiologies after acquired neurological and other medical disorders have been ruled out. A large number of relatively rare congenital neurodevelopmental conditions that include psychosis have been described. Clear guidance on the neuropsychiatric evaluation and differential diagnosis of these conditions is difficult to find in standard textbooks.

**OBJECTIVE:** To address this dearth of information we set out to concisely describe the neurodevelopmental disorders in the differential diagnosis of psychosis, their neurodiagnostic and laboratory evaluations, and relative prevalence.

**METHODS:** A literature search was conducted for disorders that may present with psychosis, utilizing PubMed and Ovid, with search terms including psychosis, metabolic, genetic, congenital and neurodevelopmental disorders. All disorders described in case reports or case series and literature reviews, including their references, were initially included. Epidemiological and diagnostic information was gathered via textbooks, OMIM, GENETESTS, and orphanet.

**Exclusion Criteria:**
1. Acquired (non-heritable/non-congenital) disorders
2. Fewer than 3 cases reported with psychosis
3. Poorly described disorders

**Analysis:** Disorders were categorized as follows:
1. By the presence of one or more of 20 associated signs (Table One)
2. By prevalent (> 1/10,000; 1/10,000-1/50,000; <1/50,000) prevalence
3. By unique phenotypic features ("Doorway Diagnoses”—Table Two)

**RESULTS:** We identified 61 congenital disorders that may present from childhood through middle age and include psychosis.

- 44 disorders (72%) have prominent associated neurological features that facilitate differential diagnosis.
- 17 disorders have readily recognizable unique phenotypes.
- 44 disorders may present without mental retardation.
- 52 disorders (85%) have characteristic laboratory features.
- 52 have known genetic loci and 3 disorders have loci yet unknown.
- 5 disorders were due to chromosomal nondisjunction.

**DISCUSSION:**
1. Case-report based research such as this is limited by difficulty in determining whether a reported relationship is coincidental or causal.
2. The cost of doing an exhaustive laboratory evaluation of all possible disorders that could result in psychosis would be astronomical. A coherent neuropsychiatric approach, such as the one presented here, increases cost savings by providing a probability-guided, examination-based approach to focus the workup.
3. Accurate neuropsychiatric diagnosis guides genetic counseling and treatment planning.
4. Studying neuropsychiatric disorders of known etiology that include psychosis will ultimately lead to research aimed at understanding the etiology of psychotic symptoms in Axis I disorders.

**REFERENCES:**
2. GENETESTS: http://www.genetests.org
3. Orphanet: http://www.orpha.net

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### TABLE ONE: ASSOCIATED SIGNS

<table>
<thead>
<tr>
<th>CODE</th>
<th>DIAGNOSIS</th>
<th>WORKUP</th>
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</thead>
<tbody>
<tr>
<td>D Z</td>
<td>Dementia</td>
<td>NA</td>
</tr>
<tr>
<td>M</td>
<td>Movement disorder</td>
<td>NA</td>
</tr>
<tr>
<td>N</td>
<td>Neuropathy</td>
<td>NA</td>
</tr>
<tr>
<td>S</td>
<td>Spasticity</td>
<td>NA</td>
</tr>
<tr>
<td>Z</td>
<td>Seizures</td>
<td>NA</td>
</tr>
</tbody>
</table>

**WORKUP CODES**

- B: Bloodwork
- G: Genetic testing
- K: Karyogram
- M: Muscle biopsy
- N: Nerve biopsy
- U: Urinalysis
- S: Stool
- P: Pathology

**NEURO CODES**

- S = Stool
- G = Genetic test/ karyotype
- M = Movement disorder
- N = Neuropathy
- D = Dementia
- Z = Seizures
- T = Tissue biopsy
- A = Autosomal
- U = Urine
- R = Reflexes
- X = X-chromosomal
- Y = Y-chromosomal
- O = Autosomal recessive
- X = X-linked recessive
- Y = Y-linked
- F = Female
- M = Male

**SUMMARY:**

The differential diagnosis includes various genetic, metabolic, and neurological disorders that can present with psychosis. Each disorder is characterized by specific signs and symptoms, genetic testing, and laboratory evaluations. The differential diagnosis is critical for accurate neuropsychiatric evaluation and appropriate treatment planning.

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**TABLE TWO: "DOORWAY DIAGNOSES”**

<table>
<thead>
<tr>
<th>CODE</th>
<th>DIAGNOSIS</th>
<th>FEATURE</th>
<th>WORKUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Cerebellar Atrophy</td>
<td>S: Ataxia</td>
<td>NA</td>
</tr>
<tr>
<td>D</td>
<td>Dementia</td>
<td>S: Incident</td>
<td>NA</td>
</tr>
<tr>
<td>F</td>
<td>Fragile X Syndrome</td>
<td>S: Short stature, learning disabilities</td>
<td>NA</td>
</tr>
<tr>
<td>K</td>
<td>Klinefelter Syndrome XXY</td>
<td>S: Tall, long arms</td>
<td>NA</td>
</tr>
<tr>
<td>S</td>
<td>Sotos Syndrome</td>
<td>S: Macroglossia, macroglena</td>
<td>NA</td>
</tr>
<tr>
<td>U</td>
<td>Usher Syndrome</td>
<td>S: Hearing loss, vision impairment</td>
<td>NA</td>
</tr>
</tbody>
</table>

**LEGEND:**

- B = Bloodwork
- G = Genetic testing
- K = Karyogram
- M = Muscle biopsy
- N = Nerve biopsy
- U = Urine
- S = Stool
- P = Pathology

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