2007-2

The Differential Diagnosis of Congenital Disorders that Include Psychosis

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Et al.

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 neuropsychiatric 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[1], GENETests[2], and orphanet[3].

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

Analysis: Disorders were categorized as follows:

1. By the presence of one or more of 20 associated signs (Table One) Disorders having major associated neurological signs are presented in Tables Two and Three along with principal diagnostic tests

TABLE ONE: ASSOCIATED SIGNS

NEURO SIGNS (Tables 2 & 3)	Dermatologic	Hepatic/Splenic Abnormality
Mental Retardation	Dysmorphic features	Endocrine Abnormality
Dementia	Abnormal Body Size	Genitourinary Abnormality
Movement Disorder	Visual Signs	Skeletal/Connective Tissue Abnormality
Neuropathy	Hearing Loss	Hematologic Disorder
Spasticity	Speech Abnormality	Vascular Pathology
Seizures	Cardiac Abnormality	None

2. By unique phenotypic features ("Doorway Diagnoses"—Table Two)

3. By prevalence (> 1/10,000; 1/10,000-1/50,000; <1/50,000)

LEGEND

PREVALENCE

- >1/10,000
- 1/10,000-1/50,000
- <1/50,000

Disorder's color indicates its prevalence.

NEURO CODES
- D = Dementia
- M = Movement disorder
- N = Neuropathy
- S = Spasticity
- Z = Seizures

WORKUP CODES
- B = Bloodwork
- G = Genetic test/ karyotype
- O = Other
- S = Stool
- T = Tissue biopsy
- U = Urine
- X = Radiology

TABLE TWO: "DOORWAY DIAGNOSES"‡

	CODE	DIAGNOSIS	FEATURE	WORKUP
MR	D	Down Syndrome	dysmorphic, short	G: trisomy 21
		Fragile X Syndrome	dysmorphic	G: CGG repeats
	SZ	Phenylketonuria	blond, blue-eyed, dry skin, musty odor	B: ↑ phenylalanine
		Coffin-Lowry Syndrome	dysmorphic, short	X: XR distal phalangeal tufting
		Prader Willi Syndrome	dysmorphic, short, obese	G: DNA methylation analysis
	S	Laurence-Moon/Biedl-Bardet	dysmorphic, short, obese	NA
		Lujan-Fryns Syndrome	dysmorphic, marfanoid	NA
		Norrie Disease	hearing and vision impairment	G: mutation analysis
		Wolfram Syndrome	hearing and vision impairment	NA
NON-MR		Klinefelter Syndrome XXY	tall, long arms	G: XXY
		Marfan Syndrome	dysmorphic, marfanoid	NA
		Oculocutaneous Albinism	hypopigmented skin and hair, blue to yellow-brown irides	G: mutation analysis
		Turner Syndrome	dysmorphic, short, obese, webbed neck	G: XO
	Z	Sturge-Weber Syndrome	port-wine stain	X: MRI/CT angiomatosis/gyral calcifications (railroad track sign)
	M	Tourette Syndrome	motor & vocal tics	NA
		Usher Syndrome	hearing and vision impairment	O: ERG & ENG
		Werner Syndrome	short, stocky, premature aging, beaked nose	NA

‡ *"Doorway Diagnoses" can be recognized by their unique phenotypic features*

TABLE THREE: DIAGNOSES WITH LESS OBVIOUS PHENOTYPES

	CODE	DIAGNOSIS	WORKUP
MR		Autism	N/A
	D S Z	Cerebrotendinous Xanthomatosis	B: ↑ cholestanol
		Kartagener Syndrome	T: mucosal biopsy
	Z	Tuberous Sclerosis	X: MRI & CT calcified nodules
	M	Homocysteinuria	B/U: ↑ methionine & homocysteine
	M	MR with Psychosis, Pyramidal Signs, and Macroorchidism (PPX-M)	G: mutation analysis
	Z	Neurocutaneous Melanosis	X: MRI melanin deposits
	M Z	Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency	U: ↑ γ-hydroxybutyric acid
NON-MR	N	Acute Intermittent Porphyria	U: ↑ porphobilinogen & δ–aminolevulinic acid
		Asperger's	NA
		Gilbert Syndrome	B: fluctuating ↑ indirect bilirubin
		Glucose-6-Phosphate Dehydrogenase Deficiency	B: RBC G6PD test
	D M	Huntington Disease	G: CAG repeats
		Neurofibromatosis, Type 1	NA
		Velo-Cardio-Facial Syndrome	G: FISH
		XXX Karyotype	G: XXX
	D N Z	Adrenoleukodystrophy	B: ↑ VLCFA
	N	Fabry Disease	B: ↓ α-galactosidase A
	D M N S	Metachromatic Leukodystrophy	B: ↓ arylsulfatase A
	N	Porphyria Variegata	U: ↑ porphobilinogen & δ–aminolevulinic acid
	D M	Wilson Disease	B: ↓ ceruloplasmin & ↑ copper
		XYY Karyotype	G: XYY
		Albright Hereditary Osteodystrophy	B: ↓calcium; ↑ phosphorus & PTH; Ellsworth-Howard test
	N	Chester Porphyria	U: ↑ porphobilinogen & δ–aminolevulinic acid
		Darier Disease	T: skin biopsy
	D M Z	Dentatorubral-Pallidolysian Atrophy (DRPLA)	G: CAG repeats
	D M Z	Fahr Disease	X: BG calcification
		Familial Hemiplegic Migraine	G: CACNA1A gene mutation
		Gaucher Disease, Type 1	B: ↓ β-glucosidase
	M Z	Gaucher Disease, Type 3	B: ↓ β-glucosidase
	D	Gerstmann-Sträussler-Scheinker	G: PRNP mutation
	N	Hereditary Coproporphyria	U/S: ↑ coproporphyrin
	D N S	Hereditary Spastic Paraparesis	G: SPG4 gene mutation
	D M Z	Kuf Disease	T: brain, muscle, or skin biopsy
	D M	Late Onset Tay-Sachs	B: ↓ hexosaminidase A activity
	D M Z	Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)	B: ↑ lactate, ↓ pyruvate
	M	Myoclonus-Dystonia	G: SGCE gene mutation
	D M Z	Nasu-Hakola	X: polycystic osseous lesions
	D M Z	Neimann-Pick Disease Type C	T: skin biopsy (fibroblasts)
	D M N Z	Neuroacanthocytosis	B: acanthocytosis; X: MRI caudate nuclei atrophy
	D M	Neurodegeneration with Brain Iron Accumulation (NBIA)	X: MRI T2 central pallidal hyperintensity with hypointense surround ('eye of the tiger' sign)
	D M N	Olivopontocerebellar Atrophy	X: MRI & CT olivopontocerebellar atrophy
	D M S	Pelizeus-Merzbacher Disease	X: MRI white matter disease
	M S	Spinocerebellar Degenerations	G: CAG repeats

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 unkown.
- 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.

CONCLUSION: As consultants frequently called upon to evaluate atypical presentations of psychosis, neuropsychiatrists should be aware of congenital disorders that can present with psychosis, however rarely. We recommend a differential diagnostic approach based on estimated prevalence of the disorders and their most prominent associated neuropsychiatric features.

REFERENCES:

1. OMIM (Online Mendelian Inheritance in Man): http://www.ncbi.nlm.nih.gov/entrez/query fcgi?db=OMIM

2. GENETests: http://www.genetests.org

3. Orphanet: http://www.orpha.net