“BENIGN AND COMMON MOVEMENT DISORDERS IN CHILDREN”

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Children with Neurological and Neurosurgical Conditions:
An Update for Pediatricians
Disclosures

I do not have relevant financial relationships with commercial interests related to the content of this presentation.
Objectives

1) Discuss clinical manifestations of the most common movement disorders in children and adolescents
2) Discuss diagnosis of these movement disorders of children and adolescents
3) Discuss medical management of these movement disorders of children and adolescents
PRAGMATIC APPROACH TO MOVEMENT DISORDERS OF CHILDHOOD AND ADOLESCENCE

Tools of the Trade

1) History
2) Family History
3) Examination
4) Videotaping
5) Cerebrospinal Fluid Analysis
6) Genetic Testing
BIOGENIC AMINE METABOLISM

Guanosine triphosphate (GTP) → **GTP-1 cyclohydrolase (GTPCH-1)** → Neopterin ← → Dihydroneopterin-triphosphate

Dihydroneopterin-triphosphate → **6-Pyruvoyl-tetrahydropterin synthase (6-PTS)** → 6-Pyruvoyl-tetrahydropterin

6-Pyruvoyl-tetrahydropterin → **Sepiapterin reductase (SPR)** → Tetrahydrobiopterin (BH4)

Tetrahydrobiopterin (BH4) → **Dihydropteridine reductase (DHPR)** → Dihydrobiopterin (BH2) → → Biopterin

Pterin-4a-carbinolamine (PCD)
BIOGENIC AMINE METABOLISM

H. Singer et al  Movement Disorders in Childhood 2010
Biogenic Amine Metabolism in Tourette Syndrome

Ian J. Butler, MB, FRACP, Stephen H. Koslow, PhD, William E. Seifert, Jr, PhD, Richard M. Caprioli, PhD, and Harvey S. Singer, MD

Biogenic amine metabolism in the central nervous system of 9 children with Tourette syndrome was evaluated by quantitation of their metabolites in cerebrospinal fluid by a gas chromatographic/mass spectrometric method. Homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) were measured in CSF before and after oral administration of probenecid. Dopamine metabolism appeared defective, as both baseline and accumulated levels of HVA after probenecid were decreased. Serotonin metabolism also appeared defective in some patients with low baseline and low accumulated levels of 5-HIAA after probenecid. Taken together with other clinical features of this disease, the results suggest an underlying disorder of dopamine and serotonin metabolism in Tourette syndrome.

Dopaminergic Dysfunction in Tourette Syndrome

Harvey S. Singer, MD,*† Ian J. Butler, MB, FRACP,‖ Larry E. Tune, MD,*‡
William E. Seifert, Jr, PhD,‖ and Joseph T. Coyle, MD‡§

A prospective clinical and biochemical study on the effects of treatment with haloperidol has been performed in seven patients with Tourette syndrome. Pretreatment cerebrospinal fluid levels of homovanillic acid (CSF HVA) were significantly reduced in all patients, whereas 5-hydroxyindoleacetic acid was reduced in only two. With haloperidol treatment, symptoms decreased in all cases (21 to 88%) and clinical improvement was associated with an increased level of CSF HVA, often returning to the normal range. Optimal therapeutic response was found with serum levels of haloperidol between 1 and 4 ng/ml; however, disturbing side effects also occurred within this range. These results support the hypothesis that Tourette syndrome may result from a supersensitivity of dopaminergic receptors.

TOURETTE SYNDROME—NATURAL HISTORY

CO-MORBID CONDITIONS
ADHD - attention
OCD - obsessive/compulsive
SIB - self-injury
LD - learning disability
ASD - autism
BEHAV - aggression

Clinical Severity

Attention Disorder

Age (Years)

5 - 10%

Ian J. Butler, MD  Division of Child and Adolescent Neurology
Updated January 2013
Neuropsychological Characteristics of Children with Tourette Syndrome: Evidence for a Nonverbal Learning Disability?

Bonnie L. Brookshire, Ian J. Butler, Linda Ewing-Cobbs, and Jack M. Fletcher
Department of Pediatrics
University of Texas Medical School Houston

Oculomotor executive function abnormalities with increased tic severity in Tourette syndrome

Cameron B. Jeter, Saumil S. Patel, Jeffrey S. Morris, Alice Z. Chuang, Ian J. Butler, and Anne B. Sereno

Background: Reports conflict as to whether Tourette Syndrome (TS) confers deficits in executive function. This study’s aim was to evaluate executive function in youths with TS using oculomotor tasks while controlling for confounds of tic severity, age, medication, and severity of comorbid disorders. Method: Four saccade tasks requiring the executive functions of response generation, response inhibition, and working memory (prosaccade, antisaccade, 0-back, and 1-back) were administered. Twenty youths with TS and low tic severity (TS-low), nineteen with TS and moderate tic severity (TS-moderate), and 29 typically developing control subjects (Controls) completed the oculomotor tasks. Results: There were small differences across groups in the prosaccade task. Controlling for any small sensorimotor differences, TS-moderate subjects had significantly higher error rates than Controls and TS-low subjects in the 0-back and 1-back tasks. In the 1-back task, these patients also took longer to respond than Controls or TS-low subjects. Conclusions: In a highly controlled task design, the findings demonstrate for the first time that increased tic severity in TS is associated with impaired response inhibition and impaired working memory and that these executive function deficits cannot be accounted for by differences in age, medication or comorbid symptom severity. Keywords: Attention deficit hyperactivity disorder, cognitive control, executive function, n-back, obsessive-compulsive disorder, saccades.
TIC TREATMENT IN TOURETTE SYNDROME

Education
Behavioral approaches
Pharmacotherapy

1st tier
- Clonidine
- Guanfacine
- Baclofen
- Topiramate
- Levetiracetam
- Clonazepam

2nd tier
- Pimozide
- Fluphenazine
- Risperidone
- Aripiprazole
- Olanzapine
- Haloperidol
- Ziprasidone
- Quetiapine
- Sulpiride
- Tiapride

Other
- Dopamine agonists
- Tetrabenazine
- Botulinum toxin

Deep brain stimulation

H. Singer et al Movement Disorders in Childhood 2010
DEVELOPMENTAL AND BENIGN MOVEMENT DISORDERS IN CHILDHOOD

- Benign jitteriness of newborns
- Benign neonatal sleep myoclonus
- Benign myoclonus of early infancy
- Sleep related rhythmic movement disorders
- Spasmus nutans
- Paroxysmal tonic upgaze
- Benign paroxysmal torticollis
- Transient dystonia of infancy
- Shuddering attacks
- Gratification behaviors
- Stereotypic movements in healthy children
- Mirror movements
- Sandifer syndrome
CLASSIFICATION OF TORTICOLLIS

Nonparoxysmal (Nondynamic) Torticollis

1. Congenital muscular torticollis
   - Intrauterine constraint
   - Birth trauma
2. Osseous torticollis
   - Congenital
   - Traumatic
   - Inflammatory
3. Central nervous system/peripheral nervous system torticollis
   - Brain
     - Posterior fossa
     - Basal ganglia
   - Spinal cord
   - Spinal nerve root/peripheral nerve
4. Ocular torticollis
   - Superior oblique muscle palsy
   - Other ocular deviations
   - Spasmus nutans
5. Nonmuscular, soft tissue torticollis
   - Infectious

K. Tomczak and N. Rosman  J Child Neurol  2012  28(3) 365-378
CLASSIFICATION OF TORTICOLLIS

Paroxysmal (Dynamic) Torticollis

1. Benign paroxysmal torticollis
2. Spasmodic (cervical dystonia)
   Primary
   Secondary
3. Sandifer syndrome
4. Drug-induced torticollis
5. Torticollis from increased intracranial pressure
6. Torticollis as a conversion disorder

K. Tomczak and N. Rosman  J Child Neurol  2012  28(3) 365-378
ESSENTIAL TREMOR IN CHILDREN AND ADOLESCENTS

Age of onset of 45 pediatric cases with ET. Note that in 11 cases (25%) the onset was so insidious that it was not known (N/K) at what age it occurred.

E Fernandez-Alvarez and J Aicardi
Movement Disorders in Children  2001
<table>
<thead>
<tr>
<th>Type of Tremor</th>
<th>Relationship to Action or Muscle State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>When limbs are fully supported against gravity</td>
</tr>
<tr>
<td>Action</td>
<td>During movement of various types</td>
</tr>
<tr>
<td>• Postural</td>
<td>While holding a limb or body part in a position, against gravity</td>
</tr>
<tr>
<td>• Kinetic</td>
<td>With directed voluntary movement</td>
</tr>
<tr>
<td>• Intention/terminal</td>
<td>While moving the limb toward a target; this is not synonymous with dysmetria but, like dysmetria, is characteristic of cerebellar origin</td>
</tr>
<tr>
<td>• Isometric</td>
<td>While contracting muscle without an observable movement</td>
</tr>
<tr>
<td>• Task-specific tremor</td>
<td>During performance of skilled tasks such as writing or playing a musical instrument</td>
</tr>
</tbody>
</table>
## DISORDERS WITH TREMOR

Differential diagnosis between congenital nystagmus and spasmus nutans

<table>
<thead>
<tr>
<th></th>
<th>Spasmus nutans</th>
<th>Congenital nystagmus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>4mo-3y (mainly before 12mo)</td>
<td>Birth (but can be detected later)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>Negative</td>
<td>Positive or negative</td>
</tr>
<tr>
<td><strong>Nystagmus</strong></td>
<td>Asymmetric (31% unilateral)</td>
<td>Bilateral symmetric</td>
</tr>
<tr>
<td><strong>Cephalic movement</strong></td>
<td>Usually previous to nystagmus</td>
<td>Simultaneous with nystagmus</td>
</tr>
<tr>
<td><strong>Evolution</strong></td>
<td>Disappearance in 36 months</td>
<td>Persistent</td>
</tr>
</tbody>
</table>

E Fernandez-Alvarez and J Aicardi  
Movement Disorders in Children  2001
# Paroxysmal Movement Disorders

## Distinguishing Features of Kinesigenic, Nonkinesigenic, and Exertion Induced Paroxysmal Dyskinesias

<table>
<thead>
<tr>
<th>Feature</th>
<th>PKD</th>
<th>PNKD</th>
<th>PED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger</td>
<td>Movement</td>
<td>ETOH, caffeine</td>
<td>Prolonged exercise, hyperventilation</td>
</tr>
<tr>
<td>Lateralization</td>
<td>Unilateral or bilateral</td>
<td>Unilateral or bilateral</td>
<td>Unilateral or bilateral</td>
</tr>
<tr>
<td>Duration</td>
<td>Seconds to minutes</td>
<td>Minutes to hours</td>
<td>5 minutes to 2 hours</td>
</tr>
<tr>
<td>Male:female</td>
<td>4:1</td>
<td>1.4:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Onset age</td>
<td>&lt;1 year to 40 years</td>
<td>&lt;1 year to 30 years</td>
<td>2-30 years</td>
</tr>
<tr>
<td>Effective medication</td>
<td>Carbamazepine, phenytoin</td>
<td>Benzodiazepines</td>
<td>Acetazolamide, benzodiazepines</td>
</tr>
<tr>
<td>Frequency</td>
<td>Up to hundreds per day</td>
<td>Up to a few per day</td>
<td>One per day</td>
</tr>
<tr>
<td>Aura</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td></td>
</tr>
<tr>
<td>Improvement with age</td>
<td>Yes</td>
<td>Yes</td>
<td>unknown</td>
</tr>
</tbody>
</table>

H. Singer et al  Movement Disorders in Childhood 2010
PAROXYSMAL KINESIGENIC CHOREOATHETOSIS

Age of onset of first attack in 121 individuals referred with paroxysmal kinesigenic choreoathetosis. Children with onset at less than 1 year of age are most likely to have another disorder.

H. Singer et al. Movement Disorders in Childhood 2010
PROLINE-RICH TRANSMEMBRANE PROTEIN 2 GENE (PPRT2)

1) Paroxysmal kinesigenic dyskinesia
1) Benign familial infantile convulsions with choreoathetosis
HISTORICAL ASPECTS OF RHEUMATIC FEVER

Group A Streptococcal Infection

Inappropriate immune response

Carditis

Recurrent episodes of Acute Rheumatic Fever

Rheumatic Heart Disease

Group A Streptococci

e.g. Streptococcal pharyngitis ("Strep throat")

Acute Rheumatic Fever
HISTORICAL ASPECTS OF RHEUMATIC FEVER
## ATAXIA IN CHILDHOOD

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic Acute ingestion</td>
<td>Alcohol, anticonvulsants, antihistamines, benzodiazepines</td>
<td>Toddlers – accidental ingestion; Adolescents – substance abuse. Mental status changes common, urine/serum toxicology screen in Emergency Department may detect unsuspected ingestions.</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Acute cerebellar ataxia</td>
<td>Symmetric cerebellar findings, gait impairment, truncal ataxia, titubation, nystagmus. Mental status normal. Usually post-infectious. Consider opsoclonus myoclonus ataxia syndrome.</td>
</tr>
<tr>
<td>Trauma/Vascular</td>
<td>Stroke, verteobasilar dissection</td>
<td>Consider after neck trauma or if hypercoagulable.</td>
</tr>
<tr>
<td><strong>Recurring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Many inborn errors of metabolism may occur intermittently</td>
<td>Can be triggered by intercurrent illness.</td>
</tr>
<tr>
<td>Migrainous</td>
<td>Basilar migraine, benign paroxysmal vertigo</td>
<td>Initial episode suggests focal pathology and in the young child, headache may not be prominent. Imaging needed to rule out other treatable causes.</td>
</tr>
<tr>
<td>Episodic Ataxias</td>
<td>Episodic Ataxias Type I and II</td>
<td>Bouts of dysarthria, gait ataxia. Sometimes triggered.</td>
</tr>
<tr>
<td>Functional</td>
<td>Psychogenic Movement Disorders</td>
<td>Gait disturbance or abnormal tremor-like movements which do not conform to usual pattern of disease and are not supported by typical neurological examination findings. Sudden onset, dramatic or variable symptoms. See chapter 19 Psychogenic Movement Disorders.</td>
</tr>
<tr>
<td><strong>Subacute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillain Barre Syndrome, including Miller Fischer Variant</td>
<td>Oculomotor paresis, bulbar weakness, hyporeflexia, pain. Risk for respiratory/autonomic failure. Note – neuromuscular causes of weakness may masquerade as ataxia due to problems with limb control and gait.</td>
<td></td>
</tr>
<tr>
<td>Acute Disseminated Encephalomyelitis (ADEM)</td>
<td>Mental status changes; and multifocal neurologic deficits. Multiple discrete gray and white matter lesions on MRI.</td>
<td></td>
</tr>
<tr>
<td>Opsoclonus myoclonus ataxia syndrome</td>
<td>Truncal ataxia, myoclonus, (transient) opsoclonus, behavioral irritability. Paraneoplastic (neuroblastoma) or post-infectious.</td>
<td></td>
</tr>
<tr>
<td>Mass lesions</td>
<td>Posterior fossa neoplasms</td>
<td>Headaches, vomiting, papilledema, cranial nerve palsies.</td>
</tr>
</tbody>
</table>
Neurologic and Psychiatric Manifestations in a Family With a Mutation in Exon 2 of the Guanosine Triphosphate–Cyclohydrolase Gene

Heidi Hahn, MD; Melissa R. Trant, MS; Michael J. Brownstein, MD, PhD; R. Andrew Harper, MD; Sheldon Milstien, PhD; Ian J. Butler, MD

Objective: To investigate the range of clinical features to correlate genotypic and phenotypic manifestations in hereditary progressive and/or levodopa-responsive dystonia due to a defect in the guanosine triphosphate–cyclohydrolase (GCH1) gene.

Design and Setting: A large family from Texas was studied in an ambulatory setting by clinicians in genetics, neurology, and psychiatry using structured interviews and examinations.

Patients: The family was selected after neurometabolic investigations of a young boy (proband) with foot dystonia and fatigue and his father, who had a long history of anxiety and depression. Results of metabolic studies showed decreased levels of metabolites of biopterin and biogenic amines in cerebrospinal fluid. Subsequently, a novel mutation (37-base pair deletion) in exon 2 of the GCH1 gene was demonstrated in 11 family members. There was no observed female sex bias, but there was a wide variability of motor dysfunctions in family members. Approximately 50% had clinical deafness and a similar number had significant psychiatric dysfunction, including depression and anxiety.

Conclusion: Study of additional families with hereditary progressive and/or levodopa-responsive dystonia using modern molecular methods will be necessary to confirm the neuropsychiatric spectrum of this disorder, in which important clinical features may be unrecognized and thus inappropriately managed.

Arch Neurol. 2001;58:749-755
GUANOSINE TRIPHOSPHATE-CYCLOHYDROLASE GENE MUTATION

Pedigree of the Texas family studied. Squares indicate male members; circles, female members; solid filled shapes, individuals with gene mutation; dotted shapes, individuals undergoing testing who had negative findings for mutation; and slashed shapes, deceased family members. Arrow indicates proband.

Arch Neurol. 2001;58:749-755
GUANOSINE TRIPHOSPHATE-CYCLOHYDROLASE GENE MUTATION

Analysis of the mutation of the guanosine triphosphate-cyclohydrolase (GCH1) gene. A. Sequence profile of the wild-type (wt) allele and that of the mutated (del) allele of the proband. The deleted 37 base pairs (bp) in exon 2 of the GCH1 gene are boxed in the wt sequence and marked with an arrow in the del allele. B. Polymerase chain reaction analysis of genomic DNA samples from individuals of the family (shown are III:3, IV:5, and IV:6 of the family pedigree). The primer set for exon 2 was used. The wt gene and the del gene migrate as a 315- and 278-bp band, respectively. Pedigree symbols are explained in the legend to Figure 1. C. Predicted translational reading frames of wt and del alleles of affected individuals. The 37-bp deletion in exon 2 leads to a shift of the reading frame, which results in a premature termination codon after amino acid 159. In boldface type are the deleted DNA sequence (marked in the wt allele) and the predicted amino acid sequence resulting from the deletion.
# Biogenic Amine Metabolite and Biopterin Levels in Cerebrospinal Fluid in a Family with Guanosine Triphosphate-Cyclohydrolase Deficit

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at Study, y</th>
<th>HVA, ng/mL†</th>
<th>5-HIAA, ng/mL†</th>
<th>MHPG, ng/mL†</th>
<th>Neopterin, pmol/mL</th>
<th>Biopterin, pmol/mL</th>
<th>Neopterin-Biopterin Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family members (pedigree)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proband (IV:5)</td>
<td>13</td>
<td>25.8</td>
<td>9.5</td>
<td>7.2</td>
<td>1.1</td>
<td>5.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Father of proband (III:3)</td>
<td>42</td>
<td>15.5</td>
<td>8.3</td>
<td>8.8</td>
<td>4.8</td>
<td>6.8</td>
<td>0.71</td>
</tr>
<tr>
<td>Sister of proband (IV:6)</td>
<td>9</td>
<td>81.4</td>
<td>30.7</td>
<td>13.1</td>
<td>18.5</td>
<td>27.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Controls, age range, y†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td>. .</td>
<td>96.1 ± 13.7</td>
<td>25.4 ± 2.7</td>
<td>11.6 ± 1.0</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>≈1</td>
</tr>
<tr>
<td>11-16</td>
<td>. .</td>
<td>72.0 ± 10.2</td>
<td>24.1 ± 4.2</td>
<td>12.2 ± 1.8</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>≈1</td>
</tr>
<tr>
<td>&gt;16</td>
<td>. .</td>
<td>48.8 ± 4.4</td>
<td>20.6 ± 2.9</td>
<td>12.8 ± 1.2</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>≈1</td>
</tr>
</tbody>
</table>

*HVA indicates homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid; MHPG, 3-methoxy-4-hydroxy phenylethylene glycol; and ellipses, not applicable.
†For control subjects, data are give as mean ± SE. To convert nanograms per milliliter to micromoles per liter, multiply by 5.49 × 10⁻³ for HVA, by 5.23 × 10⁻³ for 5-HIAA, and by 5.43 × 10⁻³ for MHPG.
GUANOSINE TRIPHOSPHATE–CYCLOHYDROLASE GENE MUTATION

NEUROPSYCHIATRY

- Dystonia (2)
- Parkinsonism (1)
- Tremor (3)
- Torticollis (2)
- Cerebral palsy-like (3)
- Fatigue (3) – late afternoon

- Deafness (6)
- Depression (4)
- Anxiety (6)
- Obsessive – compulsive (1)
- Ataxia (2)
- Extensor plantars (or striatal toe) in (3)
GUANOSINE TRIPHOSPHATE–CYCLOHYDROLASE GENE MUTATION

TREATMENT

• MOTOR dysfunction and fatigue
  - levodopa – carbidopa 5-10mg/kg/day
    (low initial dose)
  - anticholinergic agents

• PSYCHIATRIC dysfunction
  - serotonin uptake inhibitors
  - serotonin/norepinephrine uptake inhibitors
CONCLUSION

AN ALGORITHM FOR DISCOVERY

1) Slow down to EXPLORE
2) READ, but not too much
3) Pursue QUALITY for its own sake
4) Look at the raw DATA
5) Cultivate smart FRIENDS
“You do not find the answer to a biological question on the basis of results that have high p-values. You do so by arriving at an unanticipated result that takes your breath away because of its simplicity and beauty.”

Oliver Lowry PhD, medical scientist
IT HELPS TO BE LUCKY – NOT SO MUCH