Diagnostic approach to the ataxic child

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Take-Home Messages

- Ataxia: different systems and courses
- Cerebellar ataxia most prevalent in children
- History + examination: most important diagnostic tools
- Neuroimaging: key role in cerebellar ataxia
- Cerebellar dysfunction: motor + cognitive

Outline

- Cerebellum: embryology and anatomy
- Definition of ataxia and its clinical findings
- Examples of pediatric ataxia
- Ataxia Rating Scales
- Treatment

Cerebellar Development

- Very long: early embryonic period => first postnatal years
- Development of cerebellum and brain stem are closely linked
- Several genes involved => wide spectrum of malformations
- Protracted development => vulnerable to several developmental disorders
Cerebellar Development: Selective Vulnerability

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Cerebellar vulnerability</th>
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</thead>
<tbody>
<tr>
<td>In utero ischemic events including perinatal asphyxia or term</td>
<td>(-) 74.7</td>
</tr>
<tr>
<td>Perinatal infections</td>
<td>+ 71</td>
</tr>
<tr>
<td>Prematurity (≤ 30 weeks GA)</td>
<td>+ 65.4</td>
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<tr>
<td>Pre-natal infections</td>
<td>++ 51.5</td>
</tr>
<tr>
<td>In particular CMV</td>
<td>++++ 60</td>
</tr>
<tr>
<td>Premature hemorrhages</td>
<td>++++ 73</td>
</tr>
<tr>
<td>Toxicity/selected drugs</td>
<td>++++ 73</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>++++ 73</td>
</tr>
<tr>
<td>CMV, cytomegalovirus; GA, gestational age.</td>
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</tbody>
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Cerebellar Anatomy

Cerebellar Anatomy


Cerebellar ↔ Cerebral Connections

Krienen FM and Buckner RL. Cortex, 2009

Cerebellar ↔ Cerebral Connections

Volpe JJ, J Child Neurol, 2009
Ataxia

- Ataxia = lack of order
- Medicine = imbalance, incoordination
- Common problem in child neurology, but broad differential diagnosis = challenging

Ataxia: Classification

Affected system
- Cerebellar
- Sensory
- Vestibular
- Optic
- Epileptic pseudoataxia
- Functional/psychogenic

Course
- Acute
- Non-progressive
- Progressive
- Intermittent
- Episodic

Diagnostic Approach

1. History
2. Examination
3. Targeted additional investigations:
   - Laboratory
   - Neuroimaging
   - Genetic
4. Diagnosis

History

1. Basic (background) history
2. Neurological history:
   - Family history
   - Past medical history
   - Social history
   - Toxin exposure, medication
   - Patient’s perception of problem

History Issues

- Not easy to differentiate static ↔ slowly progressing:
  - Short-term observation
  - Clinical heterogeneity with variable course
- Some examples:
  - Cerebellar ataxia in CDG syndrome
  - Cerebellar ataxia in coenzyme Q10 deficiency
  - Marinesco-Sjögren syndrome

Examination

Neurological
- Test for cerebellar dysfunction
- Test for other system involvement:
  - Abnormal eye movements:
    - Nystagmus
    - Ocular motor apraxia
  - Polyneuropathy
  - Spasticity
  - Encephalopathy

General
- Involvement of other organs:
  - Eye: retina, cataract, optic nerve
  - Hearing
  - Skin
  - Organomegaly

Ataxia “pure” vs. Ataxia “plus”?
Cerebellar Motor Dysfunction

- Impaired coordination and motor control:
  - Stance
  - Gait
  - Limb
  - Speech
  - Swallowing
  - Eye movements

- Trunk Ataxia

Truncal Ataxia: Gait

- Cerebellar dysfunction:
  - Wide-based
  - Irregular rhythm, irregular steps
  - Truncal titubation
  - Unilateral lesion ⇒ stumble/fall towards affected side

- Influenced by additional abnormalities:
  - Proprioceptive loss
  - Visual impairment
  - Vestibular deficit
  - Spasticity

Truncal Ataxia

- Sitting:
  - Support needed

- Stance:
  - Broad based
  - Tandem position, standing on one leg

- Romberg test: Ask patient to
  1. Stand
  2. Close eyes

  ⇒ Negative (normal) = no change
  ⇒ Positive = loss of position sense ≠ cerebellar disease

Limb Ataxia

- Dysemetria: incoordination of a limb while performing a task
- Intention tremor: amplitude ↑ as an extremity approaches the endpoint
- Dysdiadochokinesia: incoordination while performing alternating movements

Limb ataxia

- Finger-nose-test: simple, boring
- Examination should be “fun”, include activities of daily life:
  - Drawing, writing, peg-board, games, ….
Limb Ataxia

- Archimedes spiral
- Ladder

Speech

- Dysarthria = scanning speech
- Poorly modulated rate, rhythm and force

Nystagmus

- Involuntary eye movement alternating a slow and a fast component in two directions

Nystagmus

- Horizontal nystagmus => unilateral lesion:
  - Slow and coarse looking towards lesion
  - Faster and finer looking away from lesion
- Vertical nystagmus => central (brain stem/cerebellar lesion)
  - Downbeat: craniocervical junction, toxic
  - Upbeat: MS, ischemic, degenerative
Nystagmus

- Congenital or acquired impairment of voluntary horizontal saccades
- Compensatory jerky head movements to enable fixation
- Congenital: Joubert, Cogan disease
- Acquired: Ataxia telenagiectasia, AOA1, AOA2

Ocular Motor Apraxia

- Rapid
- Involuntary
- Multivectorial (horizontal + vertical)
- Chaotic/unpredictable
- Conjugate
- Opsoclonus-myoclonus syndrome (DD of acute ataxia)
Cognitive Function + Behavior

The cerebellar cognitive affective syndrome

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Cerebellar Cognitive Affective Syndrome

- Executive function
- Spatial cognition
- Language deficits
- Personality change

Schmahmann JD and Sherman JC, Brain, 1998

Dysmetria of Thought Hypothesis

- Motor system = Ataxia
- Thought and Emotion = Cerebellar cognitive affective syndrome
  - Cerebellum regulates speed, capacity, consistency and appropriateness of mental and cognitive processes

Dysmetria of Thought Hypothesis: Topography Anterior - Posterior

- Sensorimotor:
  - Predominantly anterior lobe (I – V)
- Cognitive, affective:
  - Predominantly neocerebellum (vermal + hemispheric components of VI + VII)

Dysmetria of Thought Hypothesis: Topography Medial - Lateral

- Vermis and fastigial nucleus:
  - Autonomic regulation, affect, emotionally important memory
- Cerebellar hemispheres and dentate nucleus:
  - Executive, visual-spatial, linguistic, learning and memory

Cerebellar Cognitive Affective Syndrome

- Based on observations in adults with:
  - Cerebellar stroke
  - Cerebellitis
  - Low-grade cerebellar tumors
- Concept extended to children:
  - Low-grade cerebellar tumors
  - Cerebellitis
  - Congenital non-progressive ataxia
  - Cerebellar malformations
  - Cerebellar disruptions

Schmahmann JD, Neuropsychol Rev, 2010
Cerebellar Ataxia

- Acute
- Progressive
- Non-progressive

Progressive Cerebellar Ataxia

- Long list of rare diseases
- Heterogeneous group (clinical, genetic)
- Focused diagnostic work-up
- Only few are treatable
- 40-50% without specific diagnosis
- Dominantly inherited spinocerebellar ataxias (SCA) = rare in childhood

Friedreich Ataxia

- Autosomal recessive
- Involved organs: CNS, myocardium, pancreas
- Presentation: “clumsiness”, ataxia
- Pes cavus and scoliosis = late signs
- Areflexia: already present in preclinical stage
- MRI: normal cerebellum, cervical cord atrophy
- DD: Charcot-Marie-Tooth polyneuropathy

Non-Progressive Cerebellar Ataxia

- Non-progressive “congenital” ataxia
- Cerebellar malformations:
  - Joubert syndrome, rhombencephalosynapsis, Dandy-Walker malformation
- Cerebellar disruptions:
  - Unilateral cerebellar hypoplasia, cerebellar disruption in preterm neonates

Non-Progressive “Congenital” Ataxia (NPCA)

- “Congenital” = early evidence of cerebellar ataxia, not really congenital
- No reliable data about prevalence, but more common than any defined cerebellar malformation
NPCA: Early Presentation

- Hypotonia (no weakness, normal reflexes)
- Delayed motor + language milestones
- Ataxia: not congenital, in the first year of life
- DD:
  - Variant (bottom shuffler)
  - Neuromuscular disorder
  - Syndromic (e.g. neurofibromatosis type 1)
  - Developmental delay

NPCA in Toddlers

- Situation dominated by impaired motor performance:
  - Slow, careful; avoidance of difficult tasks
  - Balance problems more evident on soft ground, changing gait direction, gait initiation/acceleration
- With age:
  - Impaired coordination more obvious
  - Delay in language milestones
  - Concerns about cognitive abilities

NPCA: Long-Term Problems

- Ataxia tends to improve
- Major limitation = intellectual disability
- Increased prevalence of seizures
- Some patients: spastic-dystonic component

NPCA: Neuroimaging Spectrum

1. Normal: most prevalent
2. Cerebellar hypoplasia
3. Mimicking cerebellar atrophy

=> Intrafamilial variability observed
=> No correlation imaging - clinical - outcome

Hypoplasia ⇔ Atrophy

Hypoplasia
- Decreased size/volume of cerebellum
- Not filling normally configured post fossa or small posterior fossa
- But: increased interfoliar spaces possible
- No evidence of progression

Atrophy
- Dilated interfoliar spaces
- Evolving, progressive
- Normal size of posterior fossa

NPCA: Neuroimaging Spectrum


Normal MRI in girl with NPCA, 2 sisters similarly affected
Cerebellar hypoplasia in boy with NPCA
Child with "static" cerebellar ataxia over years MRT: Dilated interfoliar spaces mimicking atrophy.
NPCA: Genetics

- Autosomal recessive inheritance:
  - Many familial observations
  - Some gene loci/genes (e.g. VLDLR, CA8, ZNF592, WDR81) identified in isolated NPCA or NPCA “plus” (e.g. deafness, optic atrophy, short stature)
- Few publications on families with dominant or X-linked inheritance, no genes identified

NPCA: Differential Diagnosis

- Cerebellar malformations
- Metabolic disorders: L2HGA, GA1, CDG, Glut1 deficiency, CoQ10 deficiency
- Posterior fossa midline tumor
- Infantile onset progressive ataxias: AT, GM2, INAD
- Cogan ocular motor apraxia
- Hereditary sensory neuropathies

NPCA: Diagnostic Approach

1. Brain MRI
2. α-Fetoprotein (to exclude AT)
3. Metabolic:
   - Organic acids (GA1, L2HGA)
   - Transferrin electrophoresis (CDG)
4. Genetic testing

Joubert syndrome (JS): Epidemiology

- Estimated prevalence ~ 1:80’000
- Probably underestimated
- Male ≥ female
  - Autosomal recessive with exception of rare cases following X-linked recessive
- Reported in almost all countries

JS: Neurology

- Neonatal breathing dysregulation: common
- Muscular hypotonia: always
- Ocular motor apraxia: very common
- Ataxia: always
- Intellectual disability: almost always

JS: Cognitive Function

- Normal cognitive function => very rare
- Intellectual disability, variable degree
- Prominent impairment in visuo-spatial organization, executive functions and expressive language
- Marked intrafamilial variability

Steinlin M et al, Neuropediatrics, 1997; Poretti A et al, Neuropediatrics, 2009
JS: Behavior

- No systematic studies, mostly based on observations and reports by parents
- Variability, spectrum
- Sensitivity to noise
- Usually “easy” to handle, happy child
- Minority with behavioral difficulties (hyperactivity, aggression, self-injury)

JS: Systemic Involvement

- Eyes:
  - Retinal dystrophy (~30%)
  - Colobomas (~19%)
- Kidneys:
  - Nephronophthisis (~25%)
- Liver:
  - Congenital hepatic fibrosis (~15%)
- Other:
  - Polydactyly (~20%)

Molar Tooth Sign (MTS)

MTS = diagnostic criterion

JS: Neuroimaging

- Beyond MTS and vermian hypoplasia
- Spectrum of additional posterior fossa and supratentorial findings
- Supratentorial findings common
- No neuroimaging-genotype correlation
- Intrafamilial variability
**JS: Genetics**

- All JS-genes encode for proteins of the primary cilium/centrosome => Ciliopathy
- 21 genes account for ~ 50% of patients
- Marked genetic heterogeneity
- Weak genotype-phenotype correlation

**JS: Primary Cilia**

- Key role in development and function of:
  - Retinal photoreceptors, neurons, kidney tubules, bile ducts
- In developing cerebellum and brainstem:
  - Are implicated in neuronal cell proliferation and axonal migration

**Disruptive Development of the Cerebellum**

- Cerebellar underdevelopment without direct injury of the cerebellum
- Probably most frequent type of cerebellar abnormality in preterms
- Mean gestational age: 26-28 weeks

**Disruptive Development of the Cerebellum: Neuroimaging**

- Symmetric volume reduction of the cerebellar hemispheres
- Small vermis with preserved shape
- Small brain stem with flattened anterior curvature of the pons
**Disruptive Development of the Cerebellum: Pathomechanisms**

- **Direct effects on cerebellum:**
  - Hemosiderin (blood products)
  - Infection-inflammation
  - Hypoxia-ischemia
  - Glucocorticoids
  - Undernutrition

- **Remote effects on cerebellum (impaired trans-synaptic trophic effects)**

**Blood Products**

- Infratentorial hemosiderin in preterms without cerebellar injuries, but supratentorial hemorrhages
- Continuous decline of cerebellar volume over several weeks without any typical vascular injury pattern

**Glucocorticoids Exposure**

Postnatal exposure to clinically routine doses of hydrocortisone or dexamethasone => impaired cerebellar, but not cerebral growth

**Remote Effects**

- Transsynaptic cerebro-cerebellar diaschisis involving neuronal connections between cerebrum and cerebellum
- Diaschisis = reduction of function of a part of the brain following the interruption of an afferent pathway at a remote site
- Association with supratentorial unilateral or bilateral injuries

**Motor + Cognitive Functions + Behavior**

- Motor disturbances:
  - Ataxia to mixed CP: ~ 50%

- Cognitive deficits:
  - Deficits in visual-spatial abilities, verbal fluency, reading, memory, learning: ~ 40%
  - Attentional deficits

- Behavioral deficits:
  - Socialization deficits
  - Autistic behavior: ~ 40%
Sensory Ataxia

- Less common than cerebellar ataxia
- Loss of sensory afferents (proprioceptive) = worse with eyes closed => positive Romberg test
- Areflexia or decreased reflexes

Vestibular Ataxia

- Injury of the peripheral vestibular system => nystagmus suppressed by visual fixation
- Examination with Frenzel’s goggles:
  - No visual fixation => Visually depressed nystagmus more obvious

Bilateral Vestibular Dysfunction

- Stance + gait unsteadiness, darkness and on uneven ground ↑
- Usually NO vertigo
- Examination:
  - Head impulse test bilaterally abnormal
  - Romberg positive
- Causes:
  - Toxic (gentamycin vestibulotoxicity)
  - Meningitis
  - Bilateral vestibular schwannoma (NF2)
Functional Ataxia

- Usually easy to recognize
- Inconsistent “performance”
- Abasia, astasia
- Good achievements despite “greatest difficulties”
- Often better if “distracted” = engaged with additional task (e.g. balancing + calculating)
- If dissociate disorder assumed => restraint with additional investigations


Ataxia Rating Scales

- Limited value in daily work
- Important for:
  - Natural history documentation
  - Interventional (therapeutic) studies
- Problems:
  - Time-consuming
  - Training for assessment needed
  - Limited validation in pediatric age group

Ataxia Rating Scales

- Brief Ataxia Rating Scale (BARS): 30-point total / 5 “items”
- Scale for the Assessment and Rating of Ataxia (SARA): 40-point total / 8 “items”
- International Comparative Ataxia Rating Scale (ICARS): 100-point total / 19 “items”
- Modified ICARS (MICARS): 120-point total / 16 “items”

Ataxia Rating Scales in children

- Not yet sufficiently studied in children
- Effect of gender and age (below 10 years of age)
- BARS least reliable
- SARA and ICARS reliable, applicable > 6 years

Sival DA and Bunt SR, Dev Med Child Neurol., 2009; Sival DA et al, Dev Med Child Neurol., 2011

Treatment

- Opsoclonus-myoclonus syndrome = immunomodulatory therapy
  - Should be started as soon as possible after onset of symptoms, don’t wait for surgery
  - No standard protocol
  - Most common: Prednisolone 1-2 mg/kg/d for weeks-months until symptoms improvement

Treatment

➢ Can rehabilitation help?
➢ No data for children, scarce data for adults
➢ Adults with progressive cerebellar ataxia => coordination training focused on balance + walking => improvement after 12 weeks = individuals with cerebellar damage can learn to improve their movements
➢ Transcranial magnetic stimulation?
➢ Deep brain stimulation?

Take-Home Messages

➢ Ataxia: different systems and courses
➢ Cerebellar ataxia most prevalent in children
➢ History + examination: most important diagnostic tools
➢ Neuroimaging: key role in cerebellar ataxia
➢ Cerebellar dysfunction: motor + cognitive

Ilg W et al, Neurology, 2009; Groiss SJ and Ugawa Y, Cerebellum, 2012