Sydenham's chorea
Immune modulation treatment of severely affected children

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Immune modulation treatment of severely affected children

Treatment

Clinical symptoms

Pathophysiology

References
Clinical symptoms

Chorea definition
ongoing random-appearing sequence of
one or more discrete movements

Sangr TD et al 2009
Structural/ Congenital- Hypoxic ischemic, kerenicterus

Immune/Acquired Chorea - SLE, NMDA

Genetic - DYNC1H1, NKX2.1
Sydenham’s Chorea

the child with Sydenham chorea is punished three times - once for general fidgetiness, once for breaking crockery, and once for making faces at his grandmother.
SC - clinical diagnosis

Chorea

Tics, Dystonia, Parkisonism

30% RF single item for Jones criteria

No clear criteria
Recurrence - Risk factors

Comparison between recurrent and non-recurrent patients.

<table>
<thead>
<tr>
<th></th>
<th>SC with recurrence (n = 14)</th>
<th>SC without recurrence (n = 71)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>12 (85.7)</td>
<td>46 (64.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean age at onset (years), mean ± SD</td>
<td>10.2 ± 2.6</td>
<td>11.2 ± 2.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Duration of chorea until admission (days), mean ± SD</td>
<td>18.75 ± 19.82</td>
<td>15.31 ± 20.24</td>
<td>0.59</td>
</tr>
<tr>
<td>Patients who had symptoms for 20 days and more before first admission, n (%)</td>
<td>2 (14.3)</td>
<td>17 (23.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>Time to onset of clinical recovery (days), mean ± SD</td>
<td>12.5 ± 9.1</td>
<td>21.5 ± 20.3</td>
<td>0.173</td>
</tr>
<tr>
<td>Patients who had complete remission, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In 1-6 months</td>
<td>10 (71.4)</td>
<td>67 (94.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>In 6-12 months</td>
<td>1 (7.1)</td>
<td>3 (4.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>In &gt;12 months</td>
<td>3 (21.4)</td>
<td>1 (1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Persistent chorea, n (%)</td>
<td>3 (21.4)</td>
<td>1 (1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac involvement, n (%)</td>
<td>12 (85.7)</td>
<td>62 (87.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>ASO titer at initial evaluation</td>
<td>41.54 ± 291.1</td>
<td>539.1 ± 370</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients taking regular prophylaxis, n (%)</td>
<td>9 (64.3)</td>
<td>68 (95.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe chorea, n (%)</td>
<td>2 (14.3)</td>
<td>4 (5.6)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

SD, standard deviation.

Persistent chorea
irregular penicillin prophylaxis

Gurkas E et al 2016
Penicillin prevents recurrence
Steroids don't
<table>
<thead>
<tr>
<th>I-Behavior</th>
<th>III-Motor Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Irritable behavior</td>
<td>14. Ocular pursuit</td>
</tr>
<tr>
<td>2. Attention deficit</td>
<td>15. Dysarthria</td>
</tr>
<tr>
<td>3. Hyperactivity</td>
<td>16. Chorea (face &amp; 4 limbs)</td>
</tr>
<tr>
<td>4. Obsessions</td>
<td>17. Tongue protrusion</td>
</tr>
<tr>
<td>6. Verbal fluency</td>
<td>18. Finger taps (R+L)</td>
</tr>
<tr>
<td></td>
<td>19. Leg agility (R+L)</td>
</tr>
<tr>
<td></td>
<td>20. Muscle tone (R+L)</td>
</tr>
<tr>
<td></td>
<td>21. Gait (10 m)</td>
</tr>
</tbody>
</table>

**II-Activities of Daily Living**

<table>
<thead>
<tr>
<th></th>
<th>Information obtained from patient and/or relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Dysarthria</td>
<td></td>
</tr>
<tr>
<td>8. Chorea</td>
<td></td>
</tr>
<tr>
<td>9. Handwriting</td>
<td></td>
</tr>
<tr>
<td>10. Cutting food &amp; handling utensils</td>
<td></td>
</tr>
<tr>
<td>11. Hygiene</td>
<td></td>
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<tr>
<td>12. Dressing</td>
<td></td>
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<tr>
<td>13. Walking</td>
<td></td>
</tr>
</tbody>
</table>

Teixeira ALJ, Maia DP and Cardoso F, 2005
USCRS example Tongue protrusion

0 = can hold tongue protruded for more than 1 minute
1 = can hold tongue protruded for more than 30 seconds
2 = can hold tongue protruded for more than 10 seconds
3 = can hold tongue protruded for less than 10 seconds
4 = cannot protrude tongue
46% of children had **behavioral change** (n=144)
- Emotional labiality
- Irritability
- Age-regressed behavior

Impaired **verbal fluency & comprehension**
- Correlated with motor symptoms
- Also in RF

Zomorrodi, 2006; Harsanyi 2015
Obsessive compulsive symptoms

Yale-Brown Obsessive-Compulsive Scale (n=73)

- 34% OCD (DSM-IV)
- Compulsions
  - Checking (56%)
  - Cleaning (42%)
  - Repeating (36%)
- Obsessions
  - Aggressive (63%)
  - Contamination (34%)
- ^ also in RF without SC

Asbahr, 2005; Hounie, 2004
- social phobia
  - 24%
- depression
  - 14%
- anxiety
  - 16%

Remission = persistent

Moreira et al 2014
non motor symptoms over time

ADHD
- prior to chorea (4/14)
- 60% persistent SC (n=56)

Psychosis
- Case report (n=1)
- psychiatric patients
  - higher incidence of a history of SC (n= 369)
  - higher risk of developing schizophrenia
    - prospective controlled study (n= 29)

Ridel 2010; Maia 2005; Teixeira, 2007; Wilcox 1986
Standard treatment do not alter recurrence.

Abnormal neurological history

Long term psyc issues
• Not related to chorea

Penicillin prevents recurrence

Not steroids
Auto immune Pathophysiology

streptococcus
13 year old child

ADHD?

- Tonsillitis
- Temper tantrums
- Referred: hemichorea
- Haloperidol treatment
- Insects crawling
- Haloperidol - discontinued
- Psychosis:
  - Heard voices
  - Locked doors
  - Couldn’t stay alone

Risperidone and Olanzapine - ineffective
Lab:
- Antistreptolysin titer: 722; N<200 IU/ ml
- Borderline antinuclear antibody titer: 1:200
- Mild aortic and mitral regurgitation

MRI T2 hyperintense lesion in the left caudate nucleus
Parallel and integrative processing of motor, cognitive, and psychiatric pathways

**Parallel**

- Emotional processing
- Motivation
- Cognitive & executive function
- Motor planning
- Motor execution

**Integrative:**

Emotional -> cognitive -> motor

Haber, 2003
"I go home today. They cured me using this new miracle drug. I’m afraid it’ll be years before it’s approved for humans."
Anti Basal Ganglia antibodies presence in serum from a child with SC

Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea

Christine A Kirvan¹, Susan E. Swedo², Janet S. Heuser¹ & Madeleine W. Cunningham¹

Lysoganglioside GM1

CAM 2 kinase
Anti-D1R and Anti-D2R IgG antibody titers of Sydenham’s chorea patients (n=22) and Controls (n=22).

Surface D2R IgG antibody 30% SC 9% Tourette’s syndrome
Dopamine receptor antibody ratio (D2R/D1R) correlate with neuropsychiatric symptoms (USCRS score)

Antibodies and behavior

GABHS homogenate immunized mice

IgG deposits in deep cerebellar nuclei

Increased rearing behavior

Rearing correlated with IgG deposits

Blocked with Haloperidol

Hoffman et al 2004; Brimberg et al 2012
Ben-Pazi H and Cunningham M unpublished data
Composite Measure (D1R + D2R+ LysoGN)

SC
Strep
Cont

Time (weeks)

0  2  4  8
Not one antibody

Long term psyc issues
  - Not related to chorea

Abnormal neurological history

Penicillin prevents recurrence

Not steroids
Not one antibody

Long term psyc issues

• Not related to chorea

Abnormal neurological history

familial

Penicillin prevents recurrence

Not steroids

Not one antibody

• Not related to chorea

Abnormal neurological history

familial
Treatment
Treatment

Penicillin

Acute disease

Prophylaxis
IM Penicillin G 1,200,000 U/mo
PO Penicillin V 500 mg/d
For ???
5 years
Age 21

Symptomatic

Anti epileptic drugs
Carbamazepine
Valproic acid

Antidopaminergic
Haloperidol

Immunosuppression
Plasmapheresis
IVIG
Steroids (3w)

Garvey et al. Treatment of SC with IVIG, plasma exchange, or prednisone. J Child Neurol 2005
Not one antibody

Abnormal neurological history

familial

Long term psyc issues
• Not related to chorea

Penicillin prevents recurrence

Not steroids

Standard treatment do not alter recurrence

Not one antibody
Case 3

Pulse steroids (30 mg/kg)

After 48 hours: "this is the first day that thoughts do not enter my head"

Prednisone 1 mg/kg a year

Follow up MRI T2 hypointense lesion in the left caudate -> gliosis

5-year follow up ruled out SLE.
14 y/o girl - persistent SC & behavioral problems

3 Mo after RF > personality changed

- Irritability, sensitivity, immaturity
- Deteriorated participation
  - Did not initiate activity
  - "would break into tears when requested to clear her dinner plate off the table"

Abulia: apathy with loss of initiative and spontaneous thought & emotional responses
Typical of caudate nucleus lesions (Bhatia, 1994)
Motor (USCRS)

Valproic acid

% Valproic acid over time (months)
Haloperidol -> tiredness

Motor (USCRS)
Depression (CDI)
Inattention (DBDRS)
Hyperactivity (DBDRS)

VPA + psychological therapy
HPA
Haloperidol -> tiredness
Risperidone
^ depression -> Fluoxetine

VPA + psychological therapy
HPA
Risperidone
Fluoxetine

Motor (USCRS)
Depression (CDI)
Inattention (DBDRS)
Hyperactivity (DBDRS)
Haloperidol -> tiredness
Risperidone
^ depression  -> Fluoxetine
after 6 months-> steroids (2mg/kg↓ 3mo)

Motor (USCRS)
Depression (CDI)
Inattention (DBDRS)
Hyperactivity (DBDRS)

VPA + psychological therapy
HPA
Risperidone
Fluoxetine

Steroids
resolution (motor and behavior)
Does long term treatment have long term effects? prevention? Motor psyc?
Not one antibody

Long term psyc issues
- Not related to chorea

Standard treatment do not alter recurrence

Penicillin prevents recurrence

Not steroids

Long protocol for severe Psyc sympt

Abnormal neurological history

familial
Immune modulation treatment of severely affected children

- Use USCRS
- Look for psych symptoms
- Consider underlying factors: various Ab, Genetic factors
- Consider long term steroids in selected cases

Take home message
Thank you

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