Diagnostic and therapeutic aspects of loss-of-function sodium channelopathies in the pediatric population

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Background

Brugada Syndrome  Cardiac conduction disease

Familial atrial fibrillation  Sick sinus syndrome

FEVER

Syncope  Arrhythmias  SCD/SIDS

Heterogeneous

Lack of awareness  Paucity of literature
Objective

• To study the diagnostic and therapeutic aspects of loss-of-function cardiac sodium channelopathies in children

Methods

- Age ≤16 years
- Abnormal ECG + Genotype-positivity
- +/- Cardiac symptoms/Family history

n=33 Confirmed cases

Phenocopies (genotype-negative or unknown)

n=4 Suspected cases
Results

- n=33 confirmed cases
- Age at presentation 6±5 years (median age 4.8 years)
- Male n=19, 58%
- Index case n=10, 30%

- n=4 phenocopies
- Age at presentation 6±1 years
- All males
- All index cases
Clinical presentation and symptomatology

A

Index-Sym
n=8

Index-Asym
n=2

FS-Sym
n=6

FS-Asym
n=17

B

Number of patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>5</td>
</tr>
<tr>
<td>SVA</td>
<td>3</td>
</tr>
<tr>
<td>ACA</td>
<td>3</td>
</tr>
<tr>
<td>SCD</td>
<td>2</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
</tr>
</tbody>
</table>

All 5 symptomatic in infancy
ECG characteristics

- Heart rate 91±26 bpm, PR interval 168±35 ms, QRS duration 112±20 ms and QTc 409±26 ms
- QRS duration was significantly more among symptomatic patients (121 ± 22 ms vs. 106 ± 16 ms, p=0.03)

Conduction intervals prolonged in 28 (85%) patients
Genotype-phenotype correlation

Truncation/Missense-inactive mutations more severe than missense-active mutations (Meregalli et al Heart Rhythm 2009)
Follow-up

- 4±4 years (median 2.7 years)
- ICD (n=4), pacemaker (n=2)
- Beta-blockers: alone (n=3), in combination with device (n=2)
- High dose of beta-blockers (4-6 mg/kg/day) were required
- Recurrent tachycardia (fever) related ACA/VT in an infant managed with beta-blocker and without ICD
- Severe broad-complex arrhythmias in an infant managed with beta-blockers until age 13 yrs when recurrent exercise-related monomorphic VT ensued requiring ICD

- Phenocopies: syncope + Type 1 ECG (spontaneous 1, drug challenge 3)
- ICD (n=3)
- No events on follow-up
Symptomatic 13-year old boy with recurrent monomorphic VT
Follow-up: Parental counselling

• 3 asymptomatic pts had worsening conduction delay/ST elevation during fever
• 2 of them required antiarrhythmic treatment in addition to antipyretics
A. Baseline

Asymptomatic 7-year old girl

B. Fever (38.6°C)
Cardiac events in relation to patients’ age

- 8 fever-associated events, 2 of which were vaccination related
- SCD in a male infant on the day following vaccination
Conclusions

• Loss-of-function sodium channelopathies are a potentially lethal group of disorders in children

• Fever and vaccination act as arrhythmia-triggers

• Diagnosis depends on family-history, symptomatology, ECG and genetic-testing

• Genotyping has a role in risk stratification

• Treatment: aggressive antipyretics and monitoring during fever and vaccination, beta-blockers (where suitable) and ICD for high risk cases
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