Treatment of Brugada syndrome children
when, how, whom ?

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Adult BrS patients
risk stratification based on large registries

Agreement

- Aborted cardiac arrest : ++
- Syncope: +
- Spontaneous type 1 ECG: +
- Syncope + Spontaneous type 1: ++ (also in small paediatric cohorts)

Controversial

- VT/VF inducibility: + or -

Other : fQRS, atrial arrhythmias: ?

Asymptomatic adult patients with BrS

- Brugada syndrome mean age 45 ± 15 years
- Asymptomatic patients
  - Brugada et al. 8% event rate 33 +/-39 mos
  - Priori et al. 6% event rate at 34 +/- 44 mos
  - Eckhardt et al , 1% event rate 40 +/- 50 mos
  - Giustetto et al 1% event rate 30 +/-21 mos
  - Probst et al 1.5% event rate 31 mos

  - Yearly event rates: 2.9%, 2,1%. 0.3%, 0,4%, 0.5%

Risk stratification in children with Brugada syndrome ??

Case : asymptomatic child with BS

- Asymptomatic 13 year old boy
- Family screening
- *SCN5A* mutation
- Normal baseline ECG and spontaneous type 1 ECG
- Father aborted cardiac arrest (ICD)

- Would you implant an ICD: Yes or No?

Brugada syndrome in children symptomatic patients

- **BrS is a very rare paediatric disease!**
- SCD and life-threatening arrhythmia in BrS in children are rare but do occur!

- Paediatric literature
  - Probst Circulation 2007: 11 of 30 children (13 centres)
  - Chockalingam HRS 2012 (*SCN5A* mutations): 10 of 30 children (4 centres)
  - Conte JACC 2015: 10 of 40 children (single centre)
  - Probst HRS 2016: 21 of 106 children (many centres)

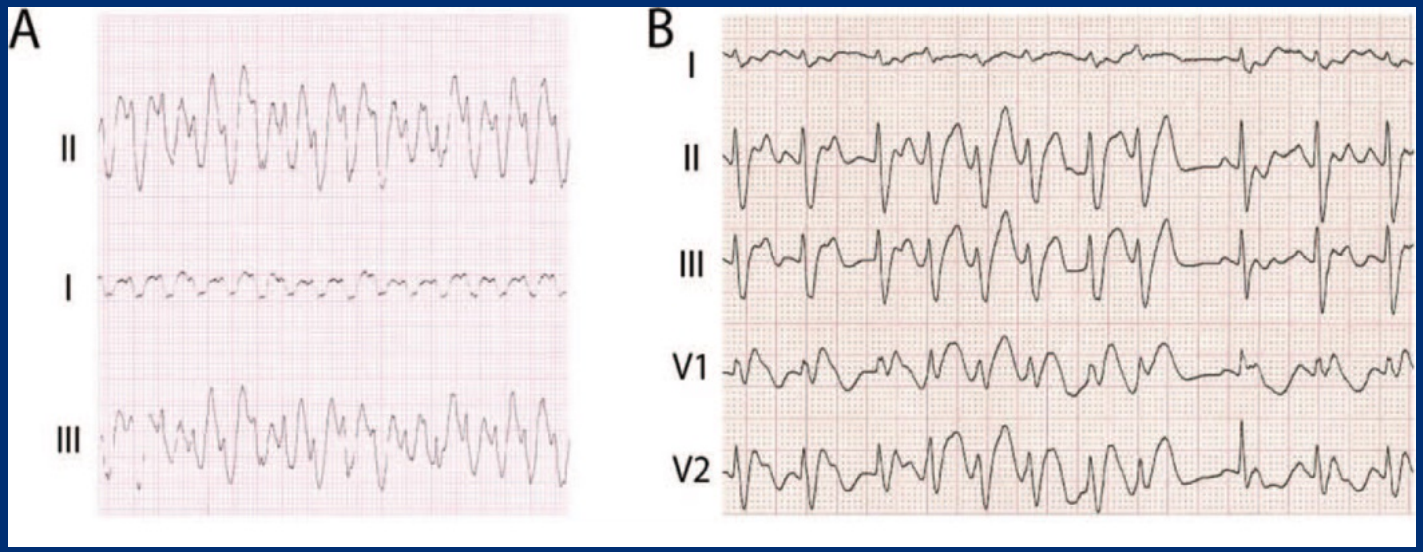
Specific issue in children with BrS children

- Treatment strategies
  - In symptomatic patients
  - In asymptomatic patients

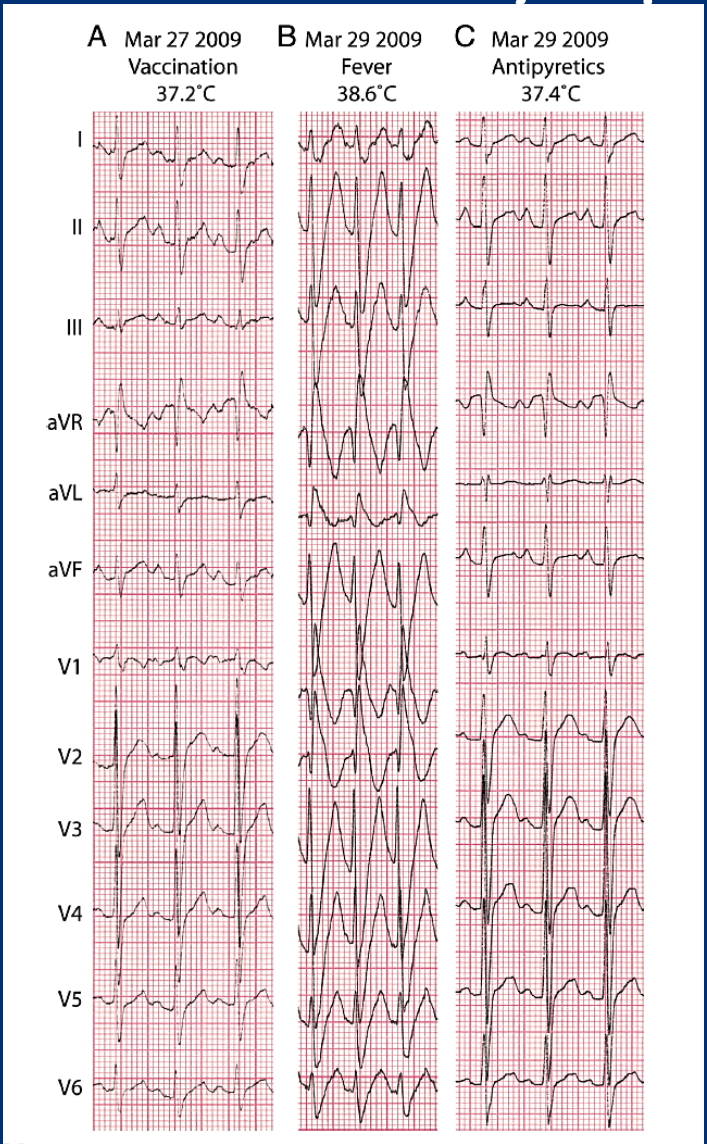
- Family screening in children
  - What age ?
  - How to screen
    - Ajmaline testing (repeated testing?)
    - Holters, Exercise test, ECG during fever
    - (EPS?)

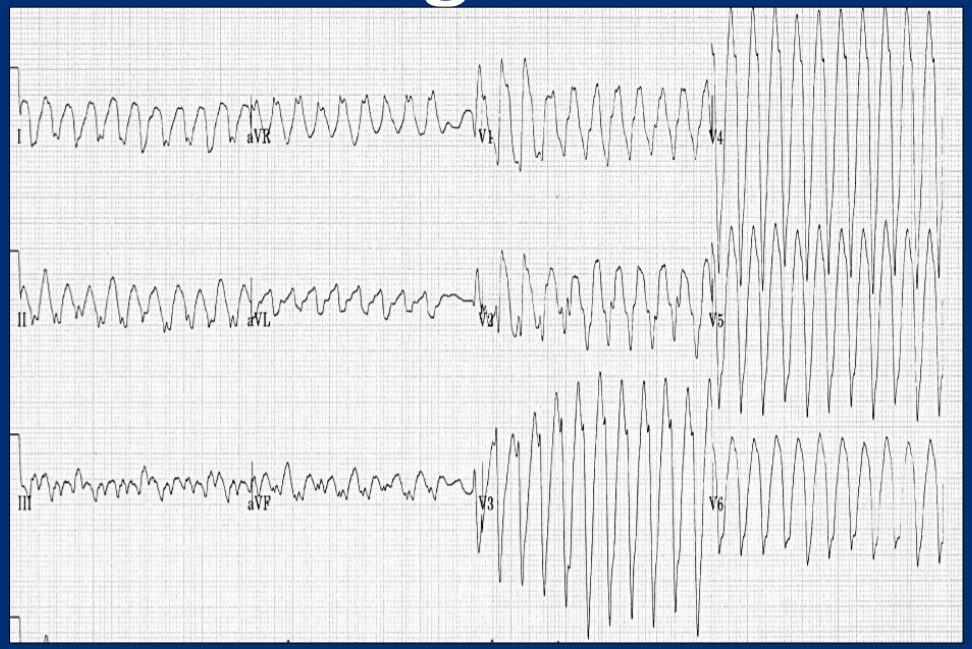
Life-threatening arrhythmia in infants and young children

- Severe phenotype!
- Girl 4 months, two weeks after vaccination, fever 39 °C, resuscitation at home, VT, defibrillated.
- ECMO for 4 days.
- Brugada syndrome and cardiac conduction delay.
- LOF *SCN5A* mutation
- FH: no SCD, arrhythmia, father and brother mutation carriers, BrS type 1 ECG, asymptomatic



ECG and symptoms during fever





Polymorphic VT during follow-up (39.5 °C)

Treatment: β-blockers, antipyretics, admission during fever, NO ICD

Age now 6-years-old

Brugada syndrome in children outcome

- 106 Pediatric pts with BrS - mean age 11 ± 6 years
- One-third spontaneous - two-third drug-induced
- Asymptomatic 75% (mostly family screening)
- Symptomatic 25% (aborted SCD/VT 6%, syncope 14%, other 5%)
- Follow-up 54 months: life-threatening arrhythmia in 10 (9%), 3 deaths, 6 syncope, 4 SVT (flutter, AT)
- 58 of 75 (77%) genetic tested patients: *SCN5A* mutation

Probst et al HRS 2016

Brugada syndrome in children outcome

- ICD in 21% patients, 2 of 11 had shocks, major adverse events in 41%
- Hydroquinidine in 10% appeared effective
- Patients with BrS/conduction disease received β-blocker
- Fever triggered 27% of life-threatening arrhythmia (LTA)
- All tested patients with LTA during FU: *SCN5A* mutation
- Risk factors for events: type 1 ECG , symptoms at diagnosis

- In symptomatic infants/children often mixed phenotype: BrS, cardiac conduction disease, atrial arrhythmias

Probst et al HRS 2016

Treatment strategies in symptomatic children with BrS patient

- Many children only at risk during fever: strict antipyretics and hospital admission during fever.
- ICD (we try to avoid ICD implantation).
- Quinidine as alternative to ICD appears to be effective: start in hospital (French experience).
- β-blockers for those with BrS/conduction delay phenotype (LOF *SCN5A*) (Dutch experience) (as adjunct or alternative to ICD).
  - Rationale: High heart rate causes more conduction delay (QRS broader) and thereby increases the risk for VT.

Chockalingam et al 2012

Outcome of children with only drug-induced BrS symptomatic and asymptomatic

- 40 Patients, <12 years, 8 ± 3 years, 60% male.
- Asymptomatic (60%) (family history of SCD).
- Aborted SCD (5%) and Syncope 20%.

- Children (compared to adults):
  1. More often sinus node dysfunction (7.5% vs 1.5%).
  2. Ajmaline challenge: caused more often sustained VT (10% vs 1.3%).

- ICD in 12 patients (30%).
- FU (83±52 months): no death, ICD appropriate shock in 1 patients, inappropriate shocks in 4 patients (33%)

- Conclusion : treatment remains individualized

Conte JACC 2014

Diagnosis and Management of Pediatric Brugada Syndrome: A Survey of Pediatric Electrophysiologists

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Table IV.

Treatments Used in Pediatric Patients with BrS

Treatment	MD's Recommendation in Symptomatic Patients	MD's Recommendation in Asymptomatic Patients
ICD	97%	24%
Antipyretics	76%	93%
Pharmacologic	31%	9%
Quinidine	58%	60%
β-blocker	37%	20%
Mexiletine	5%	–
Not specified	16%	40%
Admission during fever	3%	2%
AED	2%	2%

AED = automated external defibrillator; BrS = Brugada syndrome; ICD = implantable cardioverter defibrillator.

Bronwijn et al PACE 2015

Indications for ICD therapy in BS children?

- Class 1 (indicated): after aborted cardiac arrest.
- Class IIa (reasonable): spontaneous type 1 ECG and syncope or VT.
- Class IIb: asymptomatic with spontaneous type 1 ECG and positive EP test. This is very controversial and most centers including ours would advocate conservative management in children (and adults).
- ICD has no advantage in asymptomatic BrS with only drug-induced ST elevation!

Pacing thresholds in *SCN5A* mutation

- 3 infants undergoing ICD implantation with epicardial ventricular pacing/sensing lead (two with double SCN5A mutation)

- Acute implantation thresholds: extreme high pacing thresholds (> 8 V), even no capture, R waves very low 2-3 mV. Normalization of thresholds and R wave after 1-2 weeks in all 3 patients

- Be aware! Loss of capture in patients requiring bradycardia pacing (SND) especially during fever.

Loss-of-Function *SCN5A* Mutations Associated With Sinus Node Dysfunction, Atrial Arrhythmias, and Poor Pacemaker Capture

David Y. Chiang, PhD, **Jeffrey J. Kim, MD**, **Santiago O. Valdes, MD**, **Caridad de la Uz, MD**, **Yuxin Fan, MD, PhD**, **Jeffrey Orcutt, MD**, **Melissa Domino, RN**, **Melissa Smith, RN**, **Xander H.T. Wehrens, MD, PhD**, and **Christina Y. Miyake, MD, MS**

Background—Cardiac device implantation can be complicated by inability to adequately place leads because of significant lead capture issues. This study sought to determine whether there are genetic bases that underlie poor lead capture.

Methods and Results—Retrospective review of all patients with structurally normal hearts who underwent new device implantation at Texas Children's Hospital between 2009 and 2014 was performed. Patients with inability to capture at 10 V or a final capture threshold >3 V at 0.4 ms

patients. Three demonstrated intermittent complete loss of ventricular capture after implantation: 1 has recurrent syncope, 2 eventually died. Genetic testing performed in 10 demonstrated 7 patients with 6 distinct *SCN5A* mutations, all predicted to be severe loss-of-function mutations by

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Conclusions—This study suggests that significant capture issues at implant may be because of loss-of-function *SCN5A* mutations, providing new insights into *SCN5A* function. Recognition of this association may be critical for planning device implantation strategies and patient follow-up.

Circ Arrhythm Electrophysiol. 2015 October ; 8(5): 1105–1112. doi:10.1161/CIRCEP.115.003098.

Family screening

Diagnosis and management of asymptomatic patients

- Family screening in children
  - What age should we screen ?
  - How should we screen children?
    - Ajmaline testing (repeated testing?)
    - Holters, Exercise test, ECG during fever?
    - (EPS?)

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Studies and Labs Ordered When Evaluating a Patient for Brugada Syndrome

Studies	%
Holter	50%
Echo	45%
Drug challenge	31%
Exercise stress test	31%
Genetic testing	24%
EP study	13%
ECG + lead elevation	11%
MRI	10%
None	6%
Electrolytes	5%
Family member testing	5%

Bronwijn et al PACE 2015

Ajmaline testing in children before and after puberty

- 43 Patients (50% male) with negative ajmaline test at 11 ± 1 years.
- Repeat Ajmaline test scheduled after puberty at 19 ± 3 years.
- In 10 (23%) patients the test became positive.

Table 2. Clinical Characteristics of Patients With Positive Repeat Ajmaline Challenge

Patient No.	Sex	Age at Ajmaline Challenge, y		Family History of Sudden Death	Baseline ECG	Symptoms[a]	EPS	*SCN5A* Mutation	ICD	Appropriate ICD Intervention or Sustained VA During Follow-up
		First	Repeat							
1	Male	11	18	Yes	Normal	Syncope	Positive	No	Yes	Yes
2	Male	14	29	Yes	Type 2	Asymptomatic	Negative	No	No	No
3[b]	Female	11	18	Yes	Normal	Asymptomatic	NP	(c.[2632C > T] + [=] (p.[R878C] + [=])	No	No
4[b]	Male	14	22	Yes	Normal	Asymptomatic	NP	(c.[2632C > T] + [=] (p.[R878C] + [=])	No	No
5[b]	Female	14	25	Yes	Normal	Nocturnal agonal respiration	Negative	(c.[2632C > T] + [=] (p.[R878C] + [=])	No	No
6[b]	Female	10	18	Yes	Type 2	Asymptomatic	NP	(c.[2632C > T] + [=] (p.[R878C] + [=])	No	No
7	Female	8	17	No	Normal	Asymptomatic	NP	No	No	No
8	Female	14	22	Yes	Normal	Asymptomatic	Negative	No	No	No
9	Male	8	16	No	Type 2	Asymptomatic	NP	No	No	No
10	Female	10	24	No	Normal	Syncope	NP	c.[4719C > T] + [=] (p.Gly1573Gly); c.[274-24C > T] + [=] variant	Yes	No

Conte JAMA 2014

Case: asymptomatic child with BrS

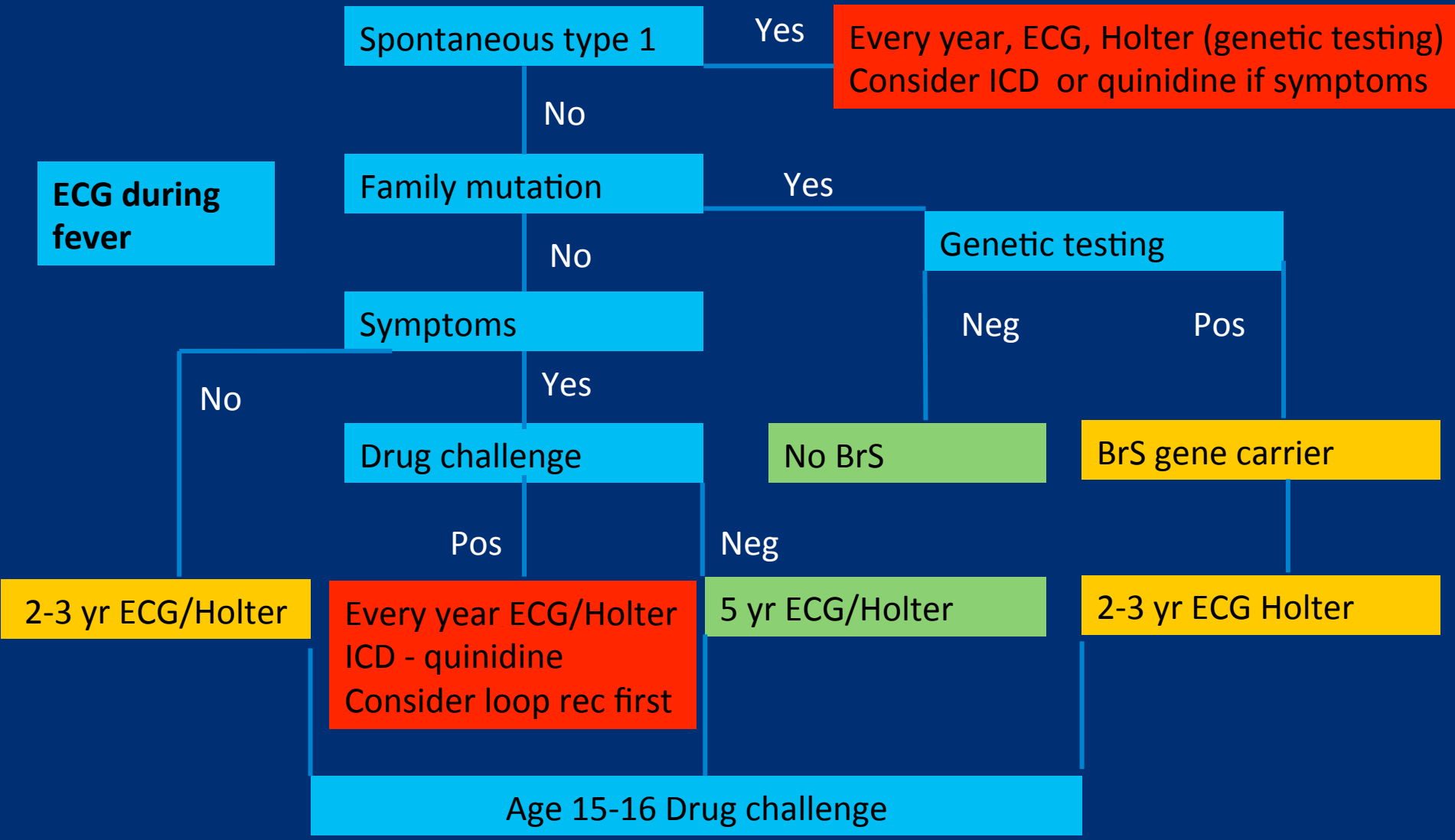
- Asymptomatic 13 year old boy
- Family screening
- *SCN5A* mutation
- Normal baseline ECG
- Spontaneous type 1 ECG
- Father aborted cardiac arrest (ICD)

- Would you implant an ICD: Yes or No

Asymptomatic child with BrS our approach

- Spontaneous type 1 ECG at baseline or during fever episodes.
- Drug avoidance and strict antipyretics during fever (consider hospital admission in case of ugly ECG).
- Close (yearly) FU.
- In case of syncope: full work-up and consider ICD or quinidine.
- In case of other symptoms, unclear “near” syncopal events: consider implantable loop recorder.

Management asymptomatic children (familial cases)

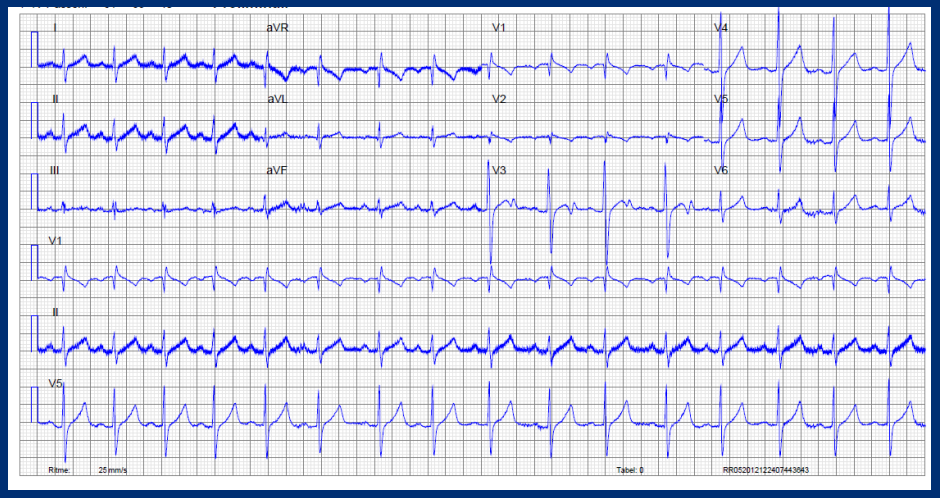


Summary

- Brugada syndrome in children is very rare.
- The majority (all?) children with symptoms have loss of function *SCN5A* mutations with mixed and sometimes very severe phenotypes.
- Fever is the most important trigger for events in children.
- ECG during fever is very useful for risk assessment and diagnosis in children.
- Ajmaline test for screening asymptomatic children before puberty is not very useful.
- β-blocker therapy can be useful in patients with BrS and cardiac conduction delay.
- ICD therapy is rarely (never?) indicated in asymptomatic children with BrS.
- Hospital admission during fever can be a good option in selected patients.

Infant with SCN5A mutation: asymptomatic child (Family screening)

37 °C



39 °C