Two Faces of Brugada Syndrome

Brugada syndrome is a genetically determined channelopathy, with an incidence of 1/1,000-10,000 people. It is responsible for 4-12% of sudden cardiac deaths (SCD) with the ventricular fibrillation (VF) mechanism. Brugada syndrome type 1 is characterized by a convex elevation of the ST segment ≥2 mm and negative T wave. The only effective treatment reducing risk of SCD for a patient with Brugada syndrome is the implantation [1,2].

Case 1: A 16-year-old boy was referred due to significant family history (SCD with VF in father at the age of 42 year, with history of repeated episodes of syncope and wheezing at night for several months, and SCD of several cousins aged 24-50 in the father’s family). The patient was asymptomatic, and denied symptoms such as syncope or palpitations. The boy’s 19-year-old brother was diagnosed with type 1 Brugada syndrome (Fig. 1), and was managed by the implantation of a subcutaneous cardioverter-defibrillator (s-ICD). Our patient’s resting ECG (along with elevated intercostal space ECG), 72-hour Holter ECG exercise test and echocardiographic examination showed no significant deviations. Ajmaline provocation test was performed. Genetic testing including analysis of 11 genes and 168 exons associated with Brugada syndrome showed the presence of a likely pathogenic variant in the SCN5A c.2947_2951dupGGTCT gene, p. (Leu985Valfs *162). The same mutation was also confirmed in the boy’s brother. Due to the positive genetic test result, deterioration of the patient’s quality of life, another death in the family (uncle age 58) despite the lack of clinical symptoms, the patient was implanted a s-ICD.

Case 2: An 11-year-old boy was referred with suspicion of Pediatric inflammatory multisystem syndrome temporally-associated with SARS-CoV-2 infection (PIMS-TS). The patient had temperatures up to of 39.5 °C along with nausea for 4 days, but no respiratory or cardiovascular complaints. Due to multi-ple desaturations to SpO2 92%, he required oxygen therapy. Laboratory tests revealed leukocytosis with lymphopenia and thrombocytopenia. There was an increased concentration of inflammatory markers (CRP 393. 8mg/L) and borderline concentration of troponin I (0.037ng/mL). Serum IgG antibodies against SARS-CoV-2 were positive. Echocardiographic examination revealed an uneven outline of the left coronary artery. In addition, moderate mitral, pulmonary, and tricuspid valvular regurgitation were observed. An ECG recorded during an episode of fever revealed a 2-3 mm ST-T segment elevation, such as in Brugada syndrome type 1 (Fig. 2). Treatment was done as per protocol including intravenous immunoglobulin, and later the child also received intravenous steroids. In control ECG examinations, including the examination with the V1 and V2 electro-des placed 1 and 2 intercostal spaces above the conventional site, no characteristic features of Brugada syndrome were found. A gradual improvement in the clinical condition and normalization of laboratory parameters were observed. Resting ECGs of the patient’s immediate family were normal. Patient was instructed with preventive recommen-dations as in Brugada syndrome. The boy was directed for genetic testing and he remains under cardiology follow-up.

The diagnosis of Brugada syndrome can be set after recording the characteristic morphology in lead V1 and/or V2 (or after switching these electrodes to the 2nd, 3rd intercostal space -nominal or high leads) during resting ECG spontaneously or after a drug provocation test (intravenous administration of a sodium channel blocking drug) [3]. Cardiac arrest is most often preceded by symptoms, such as: heart palpitations, syncope, and breathlessness at night. The disease is 8-times more common in males. Several genes are responsible for the disease, the most common mutations are associated with SCN5A gene, and several pathogenic variants are described. However, experts disagree on the usefulness of genetic testing. In AHA/ACC/HRS 2017 guide-lines, it is mentioned that “genetic testing may be useful in the diagnosis and care of relatives of people with Brugada syndrome.”

In asymptomatic patients diagnosed with Brugada syndrome, it is recommended to avoid drugs contraindicated in Brugada syndrome, strictly prohibit the consumption of alcohol and psychoactive substances, avoid fever, avoid heavy meals, monitor vital parameter (mainly at night) [2]. Several adult patients have been described in whom the resting ECG during the acute phase of SARS-CoV-2 disease revealed abnormalities of repolarization suggestive of Brugada syndrome, though all had fever and ionic disturbances [3-5]. In most patients, ECG changes normalized spontaneously after resolution of fever and did not cause serious ventricular arrhythmias. Our second patient had several risk factors that could have led to Brugada-like changes in ECG.
including fever, ionic disturbances (hyponatremia, hypophosphatemia), as well as damage to the myocardium itself in the course of PIMS-TS syndrome (i.e., changes in the coronary arteries) with negative family history [5-7].

In conclusion, Brugada syndrome is a disease, which, when detected too late, can result in SCD. However, as our two cases show, its diagnosis as well as the implementation of appropriate preventive therapy is not always easy.

Note: Both authors contributed equally to this work.

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REFERENCES
1. Gonzalez Corcia MC, Sieira J, Pappaert G, et al. implantable cardioverter-defibrillators in children and adolescents with Brugada syndrome. Am Coll Cardiol. 2018;71:148-57.
2. Sieira J, Brugada P. The definition of Brugada syndrome. Eur Heart J. 2017;38:3029-34.
3. Papadakis M, Papateodoroou E, Mellor G, et al. The diagnostic yield of Brugada syndrome after sudden death with normal autopsy. J Am Coll Cardiol. 2018;71:1204-14.
4. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary. Circulation. 2018;138:210-71.
5. Long B, Brady WJ, Bridwell RE, et al. Electrocardiographic manifestations of COVID-19. Am J Emerg. 2021;41: 96-103.
6. Vidovich MI. Transient Brugada-like electrocardiographic pattern in a patient with COVID-19. JACC: Case Reports. 2020; 2:1241-49.
7. van de Poll SWE, van der Werf C. Two patients with COVID-19 and a fever-induced Brugada-like electrocardiographic pattern. Neth Heart J. 2020;28:431-36. Chang D, Saleh M, Garcia-Bengo Y, et al. COVID-19 infection unmasking Brugada syndrome. Heart Rhythm Case Rep. 2020; 6:237-40.

Infantile Anti-N-Methyl-D-Aspartate Receptor Encephalitis Post-SARS-CoV-2 Infection

The spectrum of neurological conditions associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is evolving. Here, we describe a case of N-methyl-D-aspartate receptor encephalitis (NMDAR-E) with possible temporal association with SARS-CoV-2.

A 10-month-old typically developing boy presented with poor feeding and irritability for 5 days. On day 3 of illness, he developed fever and loose stools with 2 episodes of convulsions on day 5 of illness, when he was brought to our hospital. It was associated with loss of pre-morbidly normal eye contact. He had an upper respiratory tract infection (URTI) 40 days prior to illness onset. At presentation, his axillary temperature was 98.2°F, pulse rate was 92/minute, respiratory rate was 24/minute and blood pressure was 84/54 mmHg. General physical and systemic examinations were unremarkable. On neurological examination, baby was not interested in surroundings and had poor interaction with caregivers. Cranial nerve examination was unremarkable. Motor system examination revealed normal power and tone, with brisk deep tendon reflexes. Peri-oral dyskinesias and bilateral striatal toe were present. Cerebellar and meningeal signs were absent. In view of fever, diarrhea, seizures, acute onset encephalopathy with extrapyramidal movements, possibilities considered at admission were post-infectious immune-mediated conditions (central nervous system demyelination, autoimmune encephalitis, post-COVID multisystem inflammatory syndrome (MIS-C)) and inherited metabolic disorder. Prior to referral, baby had a normal cerebrospinal fluid (CSF) study and C-reactive protein (CRP) with elevated white cell count (WBC, 26×10⁹/L). Initial investigations at our center revealed elevated WBC (24×10⁹/L, N61 L30), normal CRP (1 mg/L) and procalcitonin (0.25 ng/mL). SARS-CoV-2 IgG antibodies were strongly positive (index-20.7, >1.0 positive). Erythrocyte sedimentation rate (22 mm/first hour), lactate dehydrogenase (515 U/L), ferritin (19.5 ng/mL) and echocardiography (normal) were not consistent with MIS-C.

Over the next 24 hours, extrapyramidal movements worsened with appearance of generalized and oro-linguo-buccal dystonia with athetosis. Hence, possibility of anti-NMDA encephalitis was considered. MRI brain was normal. CSF showed 20 cells (95%), sugar 65 mg/dL (blood sugar: 102 mg/dL), protein 27 mg/dL. CSF-polymerase chain reaction (PCR) was negative (Escherschia coli K1, Hemophilus influenza, Listeria monocytogenes, Streptococcus agalactiae, Streptococcus pneumonia, Cytomegalovirus, enterovirus, HSV1, HSV2, HHV6, Human parechovirus, Varicella zoster virus and Crypto-coccus neoformans/gattii). CSF sample for NMDA antibodies was sent to the laboratory.

Child was started on intravenous immunoglobulin (2 g/kg) and pulse methylprednisolone (30 mg/kg/day for 5 days) on day 8 of illness. CSF sample was reported strongly positive for anti-NMDA antibodies ( indirect immunofluorescence assay). Computed tomography (CT) of abdomen and pelvis for tumor screening was negative. By day 5 of pulse steroids, there was no improvement in extrapyramidal movements or encephalopathy. Considering severe infantile form of anti-NMDAR encephalitis poorly responsive to first line therapy, weekly rituximab infusion (375 mg/m²/dose/week for 4 doses) was initiated in the second week of illness, along with addition of azathioprine for long-term immunosuppression (2 mg/kg/day). Two weeks after last rituximab dose, baby remained encephalopathic. Extrapyramidal movements were partially controlled with clonidine, baclofen and clonazepam. In view of refractory disease, monthly cyclophos-