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RESEARCH ARTICLE

AN OVERVIEW OF BRUGADA SYNDROME

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Abstract

Brugada syndrome (BrS) is a rare inherited cardiac disease identified in the late 20th century, seen majorly in younger people in which males are mostly affected. Major cause includes autosomal dominant mutations in the SCN5A gene. ECG findings are helpful in disease identification. 13 types of BrS are presently based on gene mutations. Treatment includes Implantable cardioverter-defibrillator(ICD) and quinidine.

Introduction:-

Brugada syndrome(BrS) is a rare inherited, autosomal dominant arrhythmic disease having a major risk of Sudden Cardiac Death(SCD). It is observed that the structure of the heart is not changed but SCD is seen due to Ventricular fibrillation(VF) in patients[2]. Changes in ECG is considered as a diagnostic procedure in BrS. Genetically dominant autosomal mode affects the alpha subunit of the Na^+ channel by alteration of chromosome 3 and mutation in the SCN5A gene. It is estimated that the prevalence of BrS is about 0.5 per 1,000 in the world[4]. Family history of syncope or sudden death accounts for approximately 20% of the phenotype-positive proband[8]. Patients are followed up to 2 years for arrhythmia or SCD when they are finally diagnosed with BrS. Pharmacological treatment of BrS is not available.

History:

Twenty-eight years ago, no medical explanation was found in a small group of patients who experienced sudden deaths. Josep and Pedro Brugada first identified these patients with no structural heart disease and characteristic electrocardiogram (ECG) findings of right bundle branch block morphology with persistent STsegment elevation in the right-sided precordial leads[1].

Clinical Presentation:

Symptoms in BrS varies from one individual to other. Patients may experience major symptoms include:

1. Ventricular arrhythmias: irregular heartbeats,
2. Loss of consciousness or fainting (syncope), and sudden death,
3. Irregular heartbeats may cause difficulty breathing,
4. Asymptomatic: the patient doesn't show any symptoms.

Young people of southeast Asia have a high prevalence of special characteristic feature of BrS known as SUNDS, which is sudden unexpected nocturnal death syndrome.

SIDS which is sudden infant death syndrome is another presentation in BrS in which child dies of unknown cause within the age of 1 year[5].

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Epidemiology:
0.05% is an estimated world prevalence percentage of BrS[7]. Male cases are high accounting about 82%[6]. Southeast Asia has a high prevalence of BrS. Prevalence of BrS is 15 times greater in Thailand than worldwide prevalence. Prevalence of BrS is high in ages between 27 and 59 years[9]. It is assumed that 4-12% of all SCD is caused by BrS.

Causes:
Causes of BrS include inheritance and non-inheritance pattern.
Inheritance Pattern: Cause of BrS by inheritance pattern include autosomal dominant pattern, in which one copy of an altered gene from the parent is the reason for the occurrence of BrS.

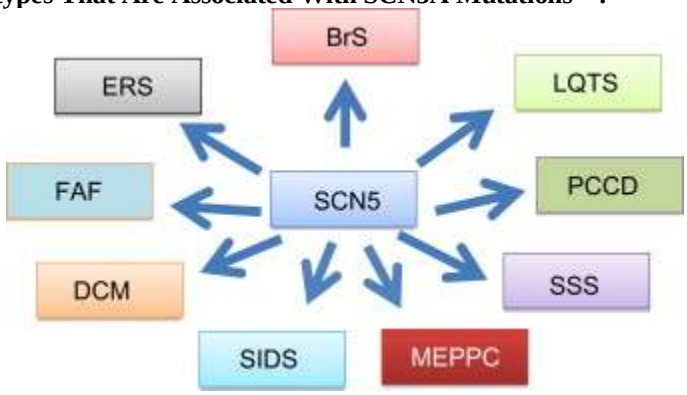
Non-Inheritance Pattern: Mutation in the gene is the main reason in Non-inheritance pattern in which the patient does not any family history of BrS[14].

Risk Factors:
Common risk factors include, – Spontaneous Type 1 BrS ECG

Aborted sudden cardiac death, History of cardiac events or syncope likely due to VT/VF, Nocturnal agonal respiration, Documented VT/VF, Late potentials on epicardial bipolar electrogram or SAECG, Short ventricular refractory period (VRP < 200 ms), T wave amplitude variability,

Fragmented QRS, Prolonged QRS duration, Early repolarization pattern in the inferolateral leads, High daily fluctuation of ECG and SAECG parameters

Multiple Cardiac Phenotypes That Are Associated With SCN5A Mutations [8]:



Long QT syndrome(LQTS); progressive cardiac conduction defects(PCCD); sick sinus syndrome(SSS); multifocal ectopic Purkinje-related premature contractions(MEPPC); sudden infant death syndrome(SIDS); dilated cardiomyopathy(DCM); familial atrial fibrillation(FAF); early repolarization syndrome(ERS).

Genetical Classification of BrS:
11-15% of BrS patients have mutations in the SCN5A gene and over 300 mutations of SCN5A have been reported [8]. It is believed that 18 other genes are also associated with BrS[11].

Brugada syndrome causative genes[8].

BrS Type	Gene Name	Chromosome	Function	% Of Probands
BrS1	SCN5A	3p 21–23	$I_{Na}k$	11-28%
BrS2	GPDIL	3p24	$I_{Na}k$	Rare
BrS3	CACNA1C	12p 13.3	$I_{Ca}k$	6.6%
BrS4	CACNB2	10p 12.3	$I_{Ca}k$	4.8%
BrS5	SCN1B	19q 13.1	$I_{Na}k$	1.1%
BrS6	KCNE3	11q 13-14	$I_{to}m$	Rare
BrS7	SCN3B	11q 23.3	$I_{Na}k$	Rare

BrS8	KCNJS	12p11.23	$I_{KATP}m$	2%
BrS9	CACNA2D1	7q21-22	$I_{Ca}k$	1.8%
BrS10	KCND3	1p13.3	$I_{to}m$	Rare
BrS11	MOGI	17p13.1	$I_{Na}k$	Rare
BrS12	SLMAP	3p21.2-p14.3	$I_{Na}k$	Unknown
BrS13	SCN2B	11q23	$I_{Na}k$	Unknown
Other Genes	KCNH2	7q36.1	$I_{Kr}m$	Unknown
	HCN4	15q24.1	$I_{f}k$	Unknown
	KCNE5	Xq 22.3	$I_{to}m$	Unknown

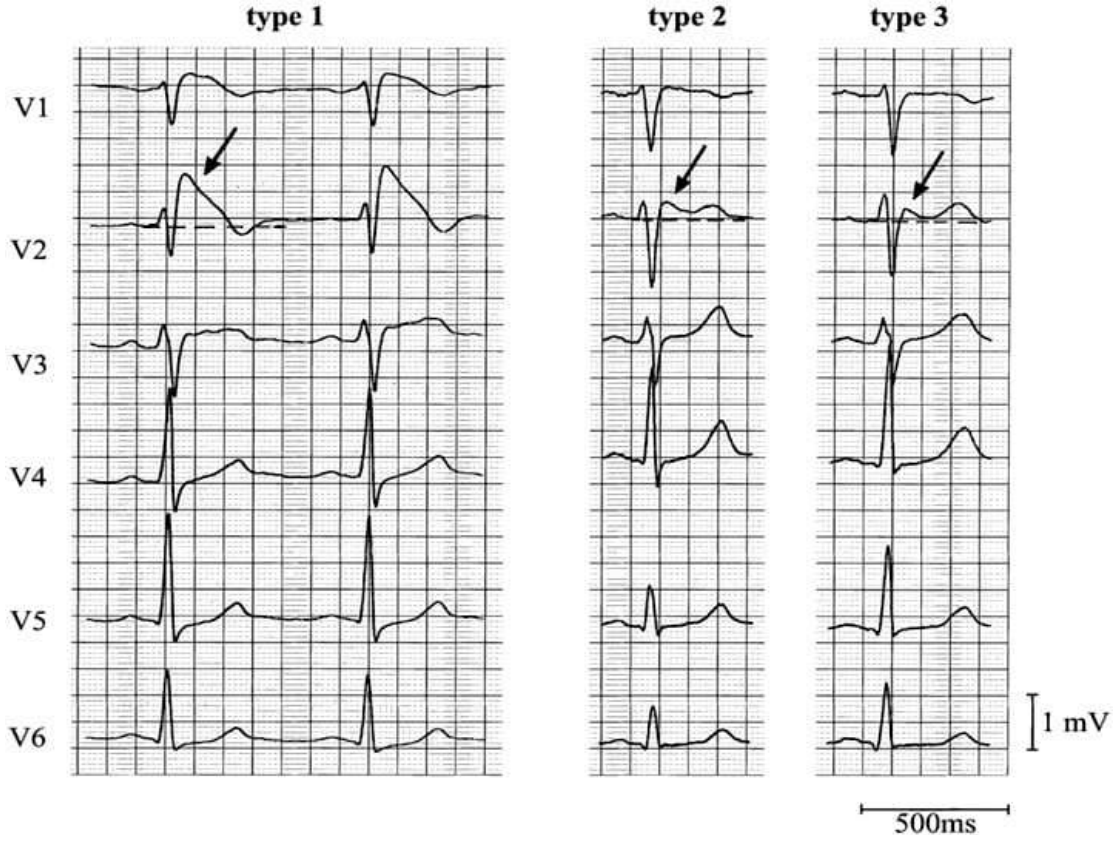
Role Of ECG In Diagnosis Of Brugada Syndrome:
ECG findings only help in identification of Brugada Syndrome. ECG criteria alone are used in the diagnosis of BrS in the first consensus report of 2002. Based on different ECG patterns three subtypes are recognised, they are:

Type 1: Cove-shaped ST elevation in right precordial leads with J wave or ST-elevation of ≥ 2mm (mV) at its peak followed by a negative T wave with little or no isoelectric interval in more than one right precordial leads V1-V3.

Type 2: The ST segments also have a high take-off but the J amplitude of ≥ 2mV gives rise to a gradually descending ST-elevation remaining ≥ 1mV above the baseline followed by a positive or biphasic T wave that results in a saddleback configuration.

Type 3: Right precordial ST elevation of <1mm of saddleback type or coved type[12].

Precordial leads of a resuscitated patient with BrS showing all 3 ECG patterns and dynamic changes over a 8-day period. Arrows indicate J waves.



According to a publication in 2005 along with ECG at least one of the six additional features is necessary for the diagnosis of BrS, they are:
documented ventricular fibrillation (VF), a family history of sudden cardiac death at <45 years, polymorphic VT, syncope or nocturnal agonal respiration (attributed to self-terminating polymorphic VT or VF). coved-type ECG in family members, inducibility of VT with programmed stimulation.

Again 2013 consensus statement does not include these six characteristics, it states only ECG criteria is essential for the diagnosis of BrS.

Diagnosis and management of patients with inherited primary arrhythmic syndromes 2013'':
BrS is diagnosed in patients with ST-segment elevation with type I morphology 2 mm in 1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

BrS is diagnosed in patients with Type 2 or Type 3 ST-segment elevation in 1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd, or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a Type 1 ECG morphology[13].

Pathophysiology:
Pathophysiology of BrS is localized to the right ventricular outflow tract (RVOT)[16] despite their models[10]. Three models will explain the electric abnormality in BrS, they are; Repolarisation, Depolarisation, Neural Crest model[10]. Epicardial action potential duration is shortened abnormally repolarisation model, whereas depolarization model revolves around conduction slowing[15]. But there is some debate on BrS is occurred by depolarization or depolarization or both[16].

Management of BrS:
Treatment of BrS is very much limited, it includes ICD and quinidine. Implantable cardioverter-defibrillator is a device implanted into the body able to perform cardioversion, defibrillation, and pacing of the heart capable of correcting cardiac arrhythmias is indicated in symptomatic BrS. In asymptomatic patients need for ICD is based on spontaneous type 1 ECG. ICD helps in preventing SCD but has risk in younger patients. ICD in the younger patient has recurrent causes of infections and risk of death is seen frequently in extraction procedures[18].

Quinidine which is a class1 anti-arrhythmic agent, used as an alternative for ICD in children, arrhythmic storms and multiple ICD discharges. In vitro studies of BrS shows that quinidine phase II re-entry and VF, by blocking Ito and IKr currents. In southeast Asia where BrS is endemic quinidine availability is not present. Thrombocytopenia, esophagitis, intolerable diarrhoea, allergic reaction, the potential for QT prolongation, aggravation of sinus node dysfunction, and torsade de pointes are the undesirable side-effects of quinidine. Few studies show in high-risk subjects quinidine cannot replace ICD as 15% of symptomatic patients with life-threatening arrhythmias events(LAE) during quinidine treatment showed recurrent LAE's, patients with BrS who had already survived an LAE, on low dose treatment of quinidine reduced recurrent LAE's[19].

Isoproterenol, cilostazol, denopamine, bepridil, disopyramide, orciprenaline and quinidine sulphate are the other medications that are available for the effective treatment of BrS.

Amiodarone, beta-blockers, calcium channel blockers, procainamide, ajmaline, flecainide, propafenone and pilsicainide are the anti-arrhythmic medications that should be avoided in the treatment of BrS[20]

Conclusion:-
BrS being a last identified cardiac disease of the 20th century has the most prevalence in south Asia mostly males in younger age. Due to many advancements in the scientific field, it made easier to find nature, pathophysiology, diagnosis, treatment of Brugada Syndrome within 25 years. As in the case of asymptomatic patients, many advances in the treatment of patients in younger ages should be done.

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