The Great Myocardial Mimic – Takotsubo Syndrome

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ABSTRACT

Takotsubo syndrome has been traditionally considered a reversible form of acute heart failure triggered by an emotional or physical stressor, mainly occurring in women of post-menopausal age and often mimicking an acute coronary syndrome. While its pathophysiology is still incompletely understood, sympathetic overstimulation is known to play a central role in the disease. The classical hallmark of the condition was the presence of wall motion abnormalities limited to the apical segments of the ventricle, leading to the so-called apical ballooning, but different patterns of wall motion abnormalities are nowadays recognised. Different definitions and diagnostic criteria for takotsubo syndrome were proposed during the last decades, reflecting the heterogeneity of the condition and the gaps in the thorough understanding of the disease. While initially it was believed to be a benign entity, takotsubo syndrome has in fact similar morbidity and mortality with acute coronary syndromes, both on short- and long-term, highlighting the importance of proper risk stratification. Many questions still remain unanswered concerning the pathophysiology of the syndrome and the optimal therapeutic strategy for these patients.

Keywords: Takotsubo, apical ballooning, sympathetic overstimulation, acute coronary syndrome.

MEDICAL VIGNETTE

A 68-year-old woman with no previous cardiovascular disease was referred to our unit for crushing substernal chest pain, which appeared three days after undergoing surgery for a hiatal hernia. The physical exam revealed moderate respiratory distress with O₂ saturation of 85%, blood pressure of 70/50 mm Hg, heart rate of 130 bpm, audible S3 with no cardiac murmurs, oliguria and mild confusion. The ECG showed a newly acquired left bundle branch block (LBBB) and the troponin came back positive, together with markedly elevated natriuretic peptides. The echocardiogram showed severe left ventricular (LV) systolic dysfunction (ejection

fraction [EF] of 15%), with severe dyskinesia of the apical segments and hyperkinetic basal segments. The patient was referred for urgent coronary angiogram, which revealed normal coronary arteries. The ventriculogram showed the typical apical ballooning pattern suggestive of takotsubo syndrome. Mechanical support with intra-aortic balloon pump was used and treatment with diuretics was initiated; two days late, circulatory support could be removed, and a beta-blocker and an angiotensin-converting-enzyme inhibitor were added. The clinical outcome was favourable, with regression of the LV systolic dysfunction at discharge (EF of 30%) and complete normalisation at six months, together with the disappearance of the LBBB.

HISTORICAL PERSPECTIVE AND NOMENCLATURE

The term "takotsubo syndrome" was first mentioned in a Japanese publication from 1990 (1), which described the case of a middle-aged woman with clinical and ECG picture suggestive of an acute myocardial infarction, but with normal coronary arteries and a particular shape of the left systolic ventriculogram resembling an octopus trap ("takotsubo" in Japanese), with complete resolution within two weeks. In the following decade, there were case reports of women over 55 years old (2-4), who, following an acute physical or emotional stress, developed a clinical and ECG picture mimicking an acute coronary syndrome, with wall motion abnormalities usually extended beyond the distribution territory of a single coronary artery, but with normal coronary arteries and complete resolution within six weeks. Although the syndrome was initially described mostly in people of Asian descent, it soon gained international awareness, leading to the proposal of the first diagnostic criteria in 2003 (5).

In 2005, Wittstein *et al.* (6) recognised the role of sympathetic overstimulation in the physiopathology of the disease, leading to catecholamine-induced reversible myocardial dysfunction. The entity received different names over the years, the most well-known being "stress cardiomyopathy", "broken heart syndrome", "apical ballooning syndrome" or "happy heart syndrome". In the following decade, different proposals for Takotsubo diagnostic criteria were published (7-13), the last one being encompassed in the first expert consensus on takotsubo syndrome (14).

EPIDEMIOLOGY

Takotsubo cardiomyopathy occurs in up to 3% of patients presenting with suspected acute coronary syndrome (15). The incidence of the syndrome appears to be increasing worldwide, probably due to a raised awareness of the disease; however, it still appears to be an underdiagnosed condition (16). Data from large registries show that up to 90% of patients are women of post-menopausal age (17, 18). The risk of developing takotsubo syndrome is five times higher in women older than 55 years than in women younger than 55 years and 10 times higher in older women in comparison to men of similar age (19). However, takotsubo syndrome has also been described in children, the youngest reported case being a premature neonate (20). Consistent data regarding racial differences in takotsubo syndrome are lacking, but studies suggest that the prevalence is higher in Asian and Caucasian people and lower in people of African descent and Hispanics (21).

ETIOLOGY

Table 1 encompasses the various potential triggering factors involved in takotsubo syndrome. Both emotional and physical events, ranging from ordinary to catastrophic, are established triggers for the disease; in a minority of patients no precipitating factor can be identified (22). Emotional stressors are not always negative, since positive emotions can also induce takotsubo cardiomyopathy – a situation described as "happy heart syndrome" (23). Physical triggers range from exacerbation of medical conditions to surgical procedures and administration of various drugs, such as chemotherapy or sympathomimetic drugs (13). Physical triggers and acute neurological disease are more common in men, while emotional triggers are more frequently encountered in women (18). Although takotsubo syndrome has been initially described as being precipitated by an acute emotional stress, data showed that in fact physical triggers are more often involved than emotional ones (18, 24).

Emotional triggers		Physical triggers	
Mood disorders	Depression	**Neurologic**	Stroke
	Suicide attempt		Epilepsy, seizure
	Divorce		Migraine
	Anxiety disorder		Cerebral bleeding
	Posttraumatic stress disorder		Aneurysm rupture
	Move to another city	**Respiratory**	Pulmonary embolism
Psychosocial stress	Illness of a family member		Exacerbated COPD
	Death of a family member		Asthma attack
	Euthanasia of a pet		Pneumonia
	Debt		Larynx spasm
	Bankruptcy	**Digestive**	Gastrointestinal bleeding
	Job loss		Inflammatory bowel disease
	Retirement	**Infection**	Peritonitis
	Argument with family members		Sepsis
	Flooding	**Oncologic**	Cancer
	Earthquake		Chemotherapy
	Storm	**Other**	Pheochromocytoma
	Car accident		Giving birth
Happy heart syndrome	Winning a jackpot		Fractures
	Positive job interview		Surgery
	Birth of a child		Anaesthesia
	Wedding		Catecholamine administration

TABLE 1. Potential triggers in takotsubo syndrome; adapted from (14)

PATHOPHYSIOLOGY

Although not thoroughly understood, the pathophysiology of takotsubo syndrome is revol_ving around sympathetic overstimulation (6, 25). Patients with takotsubo have increased circulating levels of catecholamines released from the adrenal medulla (6), as well as high levels of norepinephrine in the coronary sinus (26), suggesting an increased local myocardial release of catecholamines. Enhanced sympathetic stimulation can induce left ventricular (LV) dysfunction through various proposed mechanisms:

1. **Direct toxicity on cardiomyocytes:** the catecholamine surge induces calcium sarcoplasmic overload, which determines contraction band necrosis (27) and impaired contractility due to ATP depletion (28). Catecholamine excess can induce oxidative stress and mediates an inflammatory reaction with subsequent release of interleukins (29).

The beta 2-adrenergic receptors are mainly expressed towards the LV apex, where sympa-

thetic innervation is the lowest (30, 31) and this receptor distribution is thought to explain the sensitivity of the apex to high levels of catecholamines and the typical apical ballooning pattern seen in takotsubo (13).

2. **Microvascular dysfunction** is believed to play a major role in the pathophysiology of takotsubo syndrome, since studies found abnormal coronary microvasculature responses (32), together with apoptosis of microvascular endothelial cells on endomyocardial biopsies (33).

3. **Multivessel coronary spasm** also plays a role (29) and induction of coronary spasm with acetylcholine testing has been found in patients with takotsubo (34).

4. **Plaque rupture and thrombosis followed by rapid lysis** was proposed as a mechanism in takotsubo (14), since coexistent atherosclerotic lesions have been reported in takotsubo patients. Furthermore, takotsubo syndrome and myocardial infarction share common clinical, ECG, and biomarkers characteristics. However, takotsubo patients usually have wall motion abnormalities extending beyond a single coronary artery distribution. Some studies using intravascular ultrasound and optical coherence tomography revealed a high prevalence of vulnerable plaques among patients with takotsubo (35, 36), but no ruptured plaques or intracoronary thrombi were observed, making a direct causal association between plaque rupture and takotsubo difficult to establish with certainty.

5. **Activation of myocardial survival pathways**: excessive levels of catecholamines trigger adrenoreceptors to switch from Gs to Gi coupling (37), with a subsequent negative inotropic response. This down-regulation is believed to be a protective mechanism, limiting the myocardial injury caused by the catecholamine surge, similar to ischemic myocardial stunning.

Several predisposing factors appear to be involved in the pathogeny of the disease. Genetic factors are thought to be involved, since there are case reports of Takotsubo in different members of the same family (38). Neuro-psychiatric disease probably plays a role because its prevalence is double among patients with takotsubo when compared with patients with acute coronary syndromes (18). Hormonal factors are thought to play a role due to the fact that the majority of patients are women of post-menopausal age. Oestrogens are known to have a va-

sodilatory effect *via* up-regulation of endothelial NO synthase (39), but a clear link between oestrogen levels and takotsubo has not been proven so far. ❑

CLINICAL PRESENTATION AND INITIAL WORKUP

The most frequent symptoms at presentation are chest pain and dyspnea, often mimicking an acute coronary syndrome. The clinical picture of takotsubo induced by physical triggers can be dominated by symptoms of the underlying illness (14). Sometimes, patients present directly with hemodynamic instability and cardiogenic shock or aborted cardiac death; however, asymptomatic cases have also been described.

The ECG on admission is usually abnormal. The most common ECG finding is ST-segment elevation, which usually appears in precordial leads, mimicking a left anterior descendent (LAD) artery occlusion, but usually with a lower amplitude in comparison to acute coronary syndromes. Other common findings are negative T waves, with higher amplitude than in acute coronary syndromes, and prolonged QT interval, usually more persistent than in acute coronary syndromes. Less common findings are the appearance of Q waves (since usually there is no focal myocardial necrosis, but rather myocardial injury and edema), ST-segment depression, left bundle branch block, fragmented QRS complex or low QRS voltage (40). All the ECG changes are dynamic, the most typical pattern being initial ST-segment elevation, followed by its resolution with progressive T-wave inversion and prolongation of the QT interval, which eventually resolve within days to weeks (41). ECG changes can persist even after normalisation of ventricular function, but they are always reversible.

Troponin and CK-MB levels are lower than in acute coronary syndromes, reflecting the existence of myocardial injury and edema rather than cardiomyocyte necrosis. On the other hand, natriuretic peptides are more elevated than in acute coronary syndromes, reflecting myocardial stunning (42). Moreover, the NT-pro BNP-to-troponin ratio appears to have good discriminatory power between the two entities (43). Some studies suggested that circulating micro-RNAs can be used to distinguish between takotsubo syndrome and myocardial infarction, as micro-RNAs

that are up-regulated by stress (miR-16, miR-26a) are elevated in takotsubo and not in acute coronary syndromes (44). Interleukin-7 levels appear to be more elevated in takotsubo than in myocardial infarction (45), but their diagnostic utility is questionable. ❑

IMAGING

Echocardiography is the most available and widely used tool for the assessment of regional wall motion abnormalities and LV function. Different patterns of wall motion abnormalities exist, allowing the classification of takotsubo syndrome into five different types (18, 46):

1. The typical form, of apical ballooning, with apical akinesia/dyskinesia and hyper-contractile basal segments (∼ 80% of cases)
2. The mid-ventricular form, with hypo/akinesia of mid ventricular segments and hypercontractile apical and basal segments (up to 15% of cases)
3. The inverted (reversed/ basal) form, with apical hyperkinesia and akinesia/hypokinesia of basal segments (2-5% of cases)
4. The focal form, with akinesia of just one segment, usually an anterolateral one (up to 1.5% of cases)
5. The atypical form, with biventricular involvement or isolated right ventricular involvement (<1% of cases)

Other echocardiographic findings are related to potential complications of takotsubo syndrome and include left ventricular outflow tract (LVOT) obstruction, significant mitral regurgitation, presence of apical thrombus or mechanical complications, such as rupture of the interventricular septum rupture or free wall. Typically, LV systolic function recovers completely in 4-8 weeks (18). LVOT obstruction in Takotsubo appears to be primarily associated with a pre-existent sigmoid-shaped septum (47, 48), which is usually related to the normal aging process, hence explaining the development of LVOT obstruction in Takotsubo, which is a disease primarily involving women of postmenopausal age. De Backer *et al.* (49) found that patients with Takotsubo complicated with LVOT obstruction are older, often have a septal bulge and have systolic anterior motion of the anterior mitral valve leaflet, causing mitral regurgitation. LVOT obstruction in Takotsubo seems to be related to a predisposing LV geometry, including sigmoid-shaped septum, small LV cavity, small outflow tract and redundant mitral valve leaflets (50).

Coronary angiography is mandatory in all patients with ST segment elevation. Patients with takotsubo syndrome usually have normal coronary arteries, but the presence of significant coronary artery stenosis does not exclude the diagnosis of takotsubo. The left ventriculography can classify takotsubo syndrome into one of the five previously described forms (Figure 1).

Cardiac magnetic resonance allows the characterisation of cardiac volumes and biventricular function, the detection of mechanical com-

FIGURE 1. Ventriculogram showing the typical apical ballooning pattern of the LV in diastole (left panel) and systole (right panel)

plications or intracavitary thrombi and characterisation of myocardial tissue (such as oedema, necrosis, fibrosis). In takotsubo syndrome late gadolinium enhancement (LGE) is usually absent, which allows the differential diagnosis with myocardial infarction and myocarditis (51). Recently established CMR criteria for the diagnosis of takotsubo syndrome include the combination of typical wall motion abnormalities, myocardial oedema and absence of LGE (52). ❑

DIAGNOSTIC CRITERIA

The diagnosis of takotsubo syndrome remains challenging, even though diagnostic criteria have been constantly refined over the years (7-13). According to the 2018 expert consensus, the proposed International Takotsubo (InterTAK) diagnostic criteria are as follows (14):

- Patients show transient left ventricular hypokinesia/ akinesia/ dyskinesia usually extending beyond a single coronary artery distribution, presenting as either apical ballooning or one of the other described wall motion patterns.
- An emotional, physical or combined precipitating factor can be determined, but this is not obligatory for diagnostic. Acute neurologic disorders or pheochromocytoma are potential triggers; in comparison, in the previous diagnostic criteria, the absence of pheochromocytoma was mandatory for a positive diagnostic of takotsubo.

- New ECG changes are usually present, but in some rare cases no ECG abnormalities can be determined.
- Co-existent significant coronary artery disease does not represent an exclusion criterion for takotsubo syndrome.
- Absence of myocarditis is mandatory for diagnostic.
- Postmenopausal women are mostly affected.

The InterTAK diagnostic score serves as a tool for assessing the likelihood of takotsubo syndrome. It consists of seven reproducible clinical and ECG parameters and it helps to guide the differential diagnosis between takotsubo syndrome and acute myocardial infarction. A score over 70 points suggests a high probability, while a score of less than 70 points suggests a low/intermediate probability of takotsubo cardiomyopathy (Table 2). ❑

OUTCOME AND COMPLICATIONS

Although initially takotsubo was considered a benign cardiomyopathy, registry data showed that in-hospital mortality was 3-5%, similarly to mortality in acute myocardial infarction treated by primary PCI (18, 53), while 30-day mortality was 5.9% (18). While takotsubo syndrome is a completely reversible entity, the high incidence of potentially life-threatening complications warrants close monitoring and early risk stratification. Frequent in-hospital complications of takotsubo syndrome are acute heart failure (12-45%), sometimes leading to cardiogenic shock (6-20%); mitral regurgitation (14-25%)

Female sex	25 points
Emotional stress	24 points
Physical stress	13 points
No ST-segment depression	12 points
Psychiatric disorders	11 points
Neurologic disorders	9 points
QTc prolongation	6 points
<70 points: *low/intermediate probability* of takotsubo	
>70 points: *high probability* of takotsubo	

TABLE 2. InterTAK diagnostic score (14)

and LVOT obstruction (10-25%) (42). Among potential arrhythmias, atrial fibrillation is the most frequently encountered (5-15%), followed by atrioventricular blocks (5%) and cardiac arrest (4-6%) (42). Interventricular septum and free wall rupture are the rarest complications (<1%) (54).

Predictors for in-hospital major adverse events outcome include physical triggers (18), LV ejection fraction (LVEF) on admission <45% (18), age >75 years (55), acute neurologic disease (56), male sex (56), right ventricular involvement (56, 57), E/e' ratio (51), reversible moderate to severe mitral regurgitation (55, 57), disproportionately high levels of troponin, natriuretic peptides or white blood cell count (58). Male sex and physical triggers are also independent predictors of in-hospital mortality (59).

Cardiogenic shock occurs in ~10% of the patients with takotsubo syndrome (18) and it is one of the main causes of mortality in the acute phase. It is associated with a high mortality not only at 60-days but also at five-year follow-up (60). Independent predictors for cardiogenic shock are physical stress, apical type of takotsubo, LVEF<45%, diabetes mellitus and atrial fibrillation on admission (60).

The long-term mortality rate in takotsubo is 5.6%/patient/year and the rate of major adverse cardiovascular events is 9.9%/patient/year (18), similarly to acute coronary syndromes (61), and it depends on the triggering factor. Takotsubo induced by physical triggers and neurologic disease is associated with higher long-term mortality than acute coronary syndromes, while emotional triggers are associated with lower mortality in the long-term (61). Independent predictors for long-term mortality are physical triggers, neurologic triggers or no detectable trigger, age >70 years, male sex, LVEF <45%, cardiogenic shock, coexistent cancer (61, 62), high Killip class on admission and diabetes mellitus (62, 63). A recent large meta-regression study (64) found that older age, physical stressors and atypical ballooning pattern are significantly associated with long-term mortality.

A large retrospective study (65) showed that 26% of patients with takotsubo syndrome developed arrhythmias, in the descending order of frequency: atrial fibrillation (6.9%), ventricular tachycardia (3.2%), atrial flutter (1.9%), ventricular fibrillation (1%). Patients with arrhythmias had increased in-hospital mortality in comparison to those without arrhythmias (65).

Several studies (66, 67) found that long-term mortality in takotsubo syndrome is higher in patients with atrial fibrillation. These results were confirmed by a meta-analysis (68), which showed that atrial fibrillation in takotsubo doubles all-cause mortality. How atrial fibrillation leads to adverse outcomes is not thoroughly understood. Proposed mechanisms for the development of atrial fibrillation in takotsubo are sympathetic overstimulation, together with electrical and structural remodelling of the left atrium with subsequent atrial dysfunction, which emerges as a consequence of the LV systolic dysfunction. Atrial fibrillation may increase mortality through rapid ventricular rate, loss of atrial pump, neurohormonal activation, development of functional mitral regurgitation, thromboembolic events (68) or because of its association with severe LV dysfunction. While systolic dysfunction in Takotsubo is reversible, studies did not focus on the connection between the duration of LV dysfunction and the persistence of atrial fibrillation; the effect of atrial fibrillation on mortality might be in fact modulated by the coexistent systolic or diastolic dysfunction of the LV. Two small studies found atrial fibrillation to be an independent predictor of long-term mortality (66, 67).

Data from a large multicenter registry showed that both short- and long-term mortality in takotsubo patients with adverse rhythm disorders (ventricular tachycardia and fibrillation, asystole, complete AV block) is higher than in patients without arrhythmias (69). Jesel et al. (70) found that cardiovascular mortality, as well as all-cause mortality at one year were higher in takotsubo patients with life-threatening arrhythmias and that reduced LVEF and QRS duration >105 ms were independent predictors of malignant arrhythmias. Another interesting finding of the study was that severe arrhythmias were limited to the acute phase of the disease, with no tendency for recurrence, unlike conduction disease which was persistent at long-term follow-up.

Recurrence rate in takotsubo is not neglectable; the disease recurs in 4-5% of cases (71) and recurrences may occur from three weeks to several years after the first episode (72). Both the trigger and the ballooning pattern may differ from the initial event (73). Recurrence is associ-

ated with the magnitude of the LV systolic dysfunction (74). ❏

TREATMENT

No prospective randomized trials have been performed in patients with takotsubo; therefore, there are no guidelines regarding therapeutic strategies for these patients. All patients should be admitted in a cardiology unit with monitoring and imaging capabilities, preferably with a catheterization laboratory since the differential diagnosis between takotsubo syndrome and myocardial infarction is often difficult.

Considering sympathetic overstimulation as a central mechanism in takotsubo, beta-blockers are a reasonable choice, especially in patients with LVEF <45%. However, they are contraindicated in severe hypotension and bradycardia, acute pulmonary edema or cardiogenic shock and should be used cautiously in bradycardic patients with QT interval >500 ms (42). ß1-cardioselective beta-blockers could be preferred (75), since experimental data showed higher concentration of ß1-adrenergic receptors in basal left ventricular segments (13). Angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) are the first-line treatment whenever there is LV systolic dysfunction, due to their effect on LV remodelling. Diuretics and nitrates are recommended in patients with signs of congestion; however, they should be avoided in case of LVOT obstruction. Some authors suggest that diuretics should be used cautiously even in patients without obvious LVOT obstruction, as there are cases with latent obstruction that can be revealed using the Valsalva manoeuvre (76).

In case of cardiogenic shock, sympathomimetic drugs should be avoided (42), given the role of catecholamines in the pathogenesis of takotsubo and their potential role of aggravating LVOT obstruction (55). The mortality rate of takotsubo patients treated with catecholamine infusion reaches 20% (18). Levosimendan could be used safely in patients with cardiogenic shock, as an alternative to sympathomimetic agents (77). Mechanical circulatory support (veno-arterial ECMO or Impella devices) can be used in a bridge-to-recovery strategy in patients with cardiogenic shock, until LV function recovers.

In case of malignant ventricular arrythmias, the role of implantable cardioverter-defibrillator is uncertain due to the reversibility of the disease. A life vest may be considered until recovery of LV function. Temporary pacemakers are indicated in case of haemodynamically significant bradycardia (42).

Anticoagulants are recommended in case of intracavitary thrombi and may be considered in severe LV systolic dysfunction with large area of akinesia. Antiplatelet agents, along with statins, are recommended in case of co-existent coronary artery disease. Catecholamines can induce platelet activation, leading to transient thrombosis and endothelial dysfunction (75), therefore antiplatelet therapy could potentially reduce cardiac events if routinely administered (13). However, studies showed inconsistent results regarding the effect of aspirin on the reduction of major adverse cardiovascular events in takotsubo patients (78, 79), but there was no standardisation of the duration of antiplatelet therapy at discharge in registries. Since no prospective randomised trials have been conducted, no guidelines were developed regarding antithrombotic treatment in takotsubo patients.

Long-term treatment with ACEi or ARB was associated with improved survival (18), an effect that was not observed for treatment with beta-blockers. Renin-angiotensin-aldosterone system inhibitors seem to reduce recurrence rate, while beta-blocker therapy after discharge does not prevent recurrences (80).

While psychological distress is known to play a role in the pathogenesis of takotsubo, the use of anti-depressants or other psychiatric drugs in these patients is controversial (75), since most of these drugs' mechanism of action implies decrease of catecholamine reuptake, thus potentially increasing the risk of takotsubo occurrence. ❏

CONCLUSION

Originally described as a reversible cardiomyopathy often mimicking an acute myocardial infarction, takotsubo syndrome is in fact a heterogenous entity, with various phenotypes and triggered by various stressors. Once believed to be a benign condition, it is nowadays proved to be life-threatening, with similar morbidity and mortality with acute coronary syndromes, both

on short- and long-term. This highlights the importance of a proper initial risk stratification, in order to identify patients in need of close monitoring and intensive treatment. In fact, takotsubo syndrome and acute coronary syndromes have significant overlap in terms of clinical presentation, ECG, echocardiographic findings, biomarkers, complications and prognosis. Moreover, the presence of coronary artery disease is not an exclusion criterion for takotsubo syndrome anymore, thus making the differential diagnosis between the two entities even more difficult.

While sympathetic overstimulation is known to play a central role in the pathophysiology of the disease, the complex interplay between increased circulating catecholamines, neuro-psychiatric disease and reversible myocardial injury is still incompletely understood. Standard heart failure treatment (both pharmacologic and device therapy) is empirically recommended for patients with takotsubo, but prospective randomised trials are highly necessary. However, the use of sympathomimetic drugs should be avoided in the well-established setting of sympathetic overstimulation. During the last decade there have been several multicenter registries on takotsubo, on one side leading to an increased awareness of the disease, on the other side raising more questions about its mechanisms and outcome. There is much left to be uncovered concerning the pathophysiology and optimal therapeutic strategies of this heterogenous condition. ❑

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