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An Isolated Atrial Septal Aneurysm and its morphological types in Adult with Migraine patients: A Trans-Thoracic-Two-Dimensional Echocardiography Study.

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Abstract: An atrial septal aneurysm is a rare but well recognized cardiac abnormality of uncertain clinical relevance. Migraine has long been considered a risk factor for stroke. ASA is often observed in young patients with ischemic stroke and is frequently associated with other conditions potentially leading to embolism. The aim of the study is to find the prevalence and morphological types of Isolated ASA in adult patients with migraine in south India. During study period we performed TTE in 180 consecutive patients and diagnosis of ASA was performed according to Alexander Olivares-Reyes criteria. The prevalence of isolated ASA was higher in patients with migraine with aura (34.28%) than in patients with migraine without aura (9.09%) [p <.005] or in control subjects (4.71%) [p < .005]. Five different types of Isolated ASA were diagnosed in the present study and each one had echocardiographic characteristics. Type 2L (41.17%) and Type 4LR (26.47%), were most common type of ASA and both were more common in adult female patients with migraine. Our data suggest a role of ASA in the genesis of aura in patients with migraine. The present study pointed out a high prevalence of PFO in female patients with migraine with aura.

Key words: Atrial septal aneurysm, migraine, echocardiography

1. Introduction:

Migraine has long been considered a risk factor for stroke since the two conditions share some pathogenetic mechanisms such as alterations in cerebral blood flow, platelet hyperaggregability,endothelial alterations, etc [1].In addition ,stroke may occur during a typical migraine attack, and headache similar to migraine, manifests in 25% of patients with stroke [2]. The aim of the present study was to evaluate the prevalence of isolated ASA in patients with migraine. An Atrial Septal Aneurysm is a localized (saccular shape) or generalized deformity of the interatrial septum .Generally ASA is a localized deformity of the interatrial septum and occurs at the level of fossa ovalis but rarely may it involve entire atrial septum [3], which bulges into the right or left atrium or both. However, this definition of ASA is arbitrary. ASA was initially thought to be a rare congenital abnormality but with the advent of two-dimensional echocardiography and, more recently the widespread use of echocardiography (TTE and TEE) it has become more easily and more frequently identified in patients[4],[5]. Prevalence of ASA varies, but TTE studies estimate the rate to between 0.08% and 1.2% [6], [7], [8]. In a large autopsy series the prevalence reported was 1% [9]. More recent studies with TEE have shown prevalence between 2% and 10 % [10], [11], [12].

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ASA has been associated with congenital heart diseases such as patent foramen ovale, atrial septal defect, ventricular septal defect, valvular prolapse, patent ductus arteriosus, Ebstein's anomaly, tricuspid atresia and pulmonary atresia. It plays role in the genesis of aura in patients with migraine [13] and is also associated with acquired heart diseases including valvular diseases, cardiomyopathy, systemic hypertension, pulmonary hypertension, ischemic heart disease, arrhythmias, and thrombus formation. More recently a number of studies found an association between ASA and cerebrovascular events of embolic origin, including transient ischemic attacks and cerebrovascular accidents. The recent improvement in image quality of TTE and, more recently, the widespread use of TTE have made it possible to focus on the association between some cardiac abnormalities (e.g. Patent foramen ovale or ASA) and cerebral ischemic events [14]. Recent reports have pointed out a high prevalence of Patent foramen ovale (PFO) in patients with migraine with aura [15], [16]. ASA is often observed in young patients with ischemic cerebral stroke and is frequently associated with other conditions potentially leading to embolism, such as PFO, Mitral or Tricuspid Valve prolapse, atrial septal defect, endocranial vascular malformation, etc. [17],[18].

2. Material and Methods

This was a prospective, single center, longitudinal study conducted by the Department of Medicine at Chalmeda Anand Rao Institute of Medical Sciences, a semi-urban tertiary care teaching hospital - Bommakal- Karimnagar-Andhra Pradesh -India, over a period of four year from December 2009 to December 2013. The aim of the present study was to evaluate the prevalence of isolated ASA in patients with migraine. We enrolled 180 consecutive adult patients {130 women and 50 men; mean age, 35.5years (SD, 9)} with migraine but free from cerebral and cardiovascular diseases, referred or presented to our department for further evaluation in out patient department (OPD) and IPD (in patient department). One hundred and six (106) control subjects {74 women and 32 men; mean age 34 years (SD, 10)} were also included in the present study. Patients were divided into two groups: group "A" comprised 70 patients {20 men and 50 women; mean age, 33.2 years (SD, 8.1)} with migraine with aura, and group "B" consisted of 110 patients {30 men and 80 women; mean age, 36.6 years (SD, 9.1)}, with migraine without aura. Group "C" included the 106 control subjects who had no history of migraine, neurological defects, or cardiovascular disease. The diagnosis of migraine was made according to the criteria of the International Headache Society classification [19]. All patients underwent a complete clinical examination including brain computed tomography, electroencephalogram (EEG), Twelve- Lead- Surface Electrocardiography (ECG), Chest Radiography and the diagnosis of ASA was confirmed by Trans-Thoracic-Two-Dimensional Echocardiography. Information concerning current use of tobacco and oral contraceptives and a personal history of migraine was obtained (Table 4). All patients underwent: Trans-Thoracic-Two-Dimensional Echocardiography in various standard views, M-Mode, Color flow Doppler and Spectral Doppler echocardiography. The Echocardiographic studies were performed using two commercially available cardiac ultrasound systems (ESAOTE – Megas-GPX and Phillips Clear Vue 550) with 2.5 to 4 MHz phased array imaging transducers. Both systems were capable of M-Mode, color flow Doppler and Spectral Doppler echocardiography. All patients underwent standard TTE views including Parasternal long axis(PLAX), Parasternal short axis [(PSAX) at Apical , Mid Cavity and Basal level], Parasternal high short axis view (PHSX), Supra Sternal view, Apical four, five, three and two chamber views as well as Subcostal four chamber and short axis views. The studies were performed with the patient in supine and left lateral decubitus positions during quiet respiration. Particular attention was given to Subcostal views with appropriate transducer angulations to visualize the heart completely in four chamber view and the interatrial septum with its foramen ovale segment was visualized in particular. The atria, including the Atrioventricular valves (A.V. Valves), was magnified to ease the visualization of movements and measurement of ASA. Patients were placed in supine position with legs and knees flexed. They were in quiet respiration and sustained inspiration. Contrast echocardiography studies were performed with the use of agitated saline solution during TTE in patients in whom intracavitary shunt was suspected. Ten milliliters (10 ml) of vigorously agitated saline solution was injected in an antecubital vein during normal respiration and during a series of coughs or Valsalva maneuver**.** Diagnosis of PFO was made if at least 5 contrast micro bubbles were observed in the left atrium during the first three or four cardiac cycle after opacification of the right atrium either spontaneously or during Valsalva maneuver [20]. ASD was diagnosed if a "clean area" (negative effect) was produced near the interatrial septum when the right atrium was opacificated by the micro bubbles. The diagnostic criteria for ASA were made if a sacculation type of deformity in the interatrial septum or the foramen ovale region was seen. An excursion of > 10 mm beyond the plain of the atrial septum into the right or left atrium or if the sum of bilateral excursions of > 10mm was required. The minimal aneurysmal base amplitude (width) accepted in this study was 15mm in diameter. The aneurysm was observed in Subcostal, apical four-chamber and parasternal short –axis views at the level of the great vessels. Some times the bulging was also seen in apical two - and three –chamber views. All the studies were taped, and hard copies were taken for further analysis and measurements. All cases were reviewed by all observers (authors).The diagnosis of ASA was performed according to Alexander Olivares-Reyes criteria.

3. Results

Statistical analysis was performed by an analysis of variance test and by the Fisher exact test. Group A and B did not differ from each other regarding age, gender, and migraine characteristics such as history, attack duration, and therapy. The only difference concerned the attack frequency; it was significantly higher in patients in group A (Table 1). The control subjects did not show any difference, with respect to groups A and B, concerning age and gender.

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Table 1: Characteristics of study participants

Feature	*Group A (n=70)*	*Group B (n=110)*	*Group (n=106)*	*P Values*		
				Group A Versus B	*Group A versus C*	*Group B versus C*
Mean Age in year, (SD)	33.2(8.1)	36.6(9.1)	34(10)	NS	NS	NS
Sex						
- Male	54	57	60	NS	NS	NS
-Female	146	143	140	NS	NS	NS
Migraine history, year	134	114	--	NS	--	--
≤ 10 year	66	86	--	NS	--	--
≥ 10 year						
Attack Duration, hour	102	97	--	NS	--	--
≤ 24hour	98	103	--	NS	--	--
≥ 24hour						
Migraine frequency/month	18	74	--	.006	--	--
≤ 1 month	182	126	--	.003	--	--
≥ 1month						
Tobacco use						
- Yes	54.6	46	50	NS	NS	NS
- No	146	154	150	NS	NS	NS
Oral contraceptive use	46	62	56	NS	NS	NS
- Yes	154	138	144	NS	NS	NS
- No						

Isolated Atrial septal aneurysm was detected in 34 (18.88%) of 180 patients with migraine (group A plus B) and in only 5 (4.71%) of 106 control subjects ($p < .005$). When the two groups of patients with migraine were analyzed separately, isolated atrial septal aneurysm was observed in 24 (34.28%) of 70 patients of group A and in 10 (9.09%) of 110 patients of group B ($p < .005$). The difference between group A and group C was statistically significant ($p < .005$); where as no difference was observed between group B and C ($p = .9$). In group A, the ASA was associated with PFO in nine cases (37.5%); while in group B, three (30%) had PFO. In the group C, PFO was present in the unique patient with ASA. All five different types of ASA, diagnosed by TTE in the present study (Table 2 & figure 1 to 7) are as follows: Type 1R 11.76%; Type 2L 41.17%; Type 3RL 17.64 %; Type 4LR 26.47% and Type 5, 2.94%. All type of ASA had particular clinical and echocardiographic characteristics. Type 2L (41.17%) and Type 4LR (26.47%), was commonest type of ASA in the present study.

Table 2: Different Morphological type of ASA Diagnosed by TTE in present study

Type of ASA	Group "A" (n=24)	Group "B" (n=10)	Group "A" Plus "B" (n=34)
Type 1R	3 (12.5%)	1 (10%)	4 (11.76%)
Type 2L	10 (41.66%)	4 (40%)	14 (41.17%)
Type 3RL	4 (16.66%)	2 (20%)	6 (17.64%)
Type 4LR	6 (25%)	3 (30%)	9 (26.47%)
Type 5	1 (4.1%)	0	1 (2.94%)

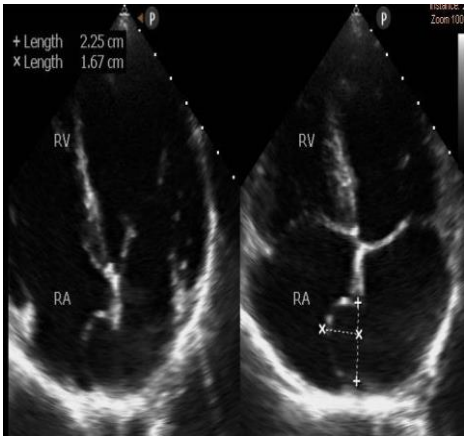

Figure 1: Inverted AP4C view shows Type 1 R ASA. [RA: Right atrium and RV: Right ventricle, AP4C: Apical four chamber]

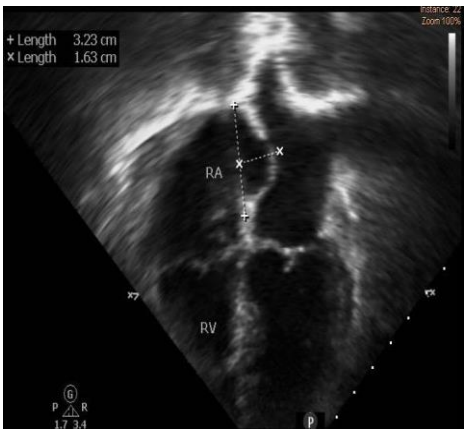

Figure 2: AP4C view shows Type 2L ASA.

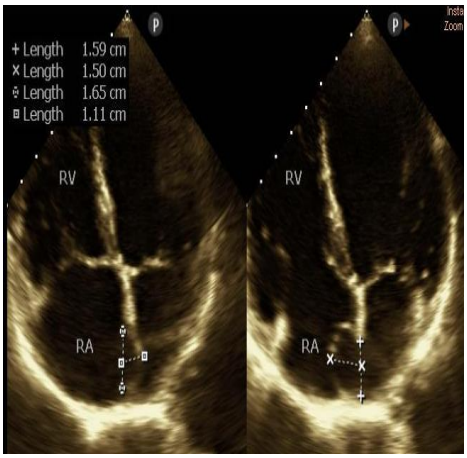

Figure 3: Type 3 RL ASA: inverted AP4C view shows, maximal excursion of aneurysm toward RA (left frame) and lesser excursion toward LA (Right frame).

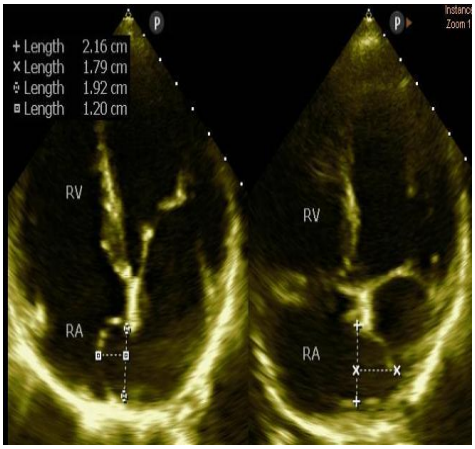

Figure 4: Type 4 LR ASA: inverted AP4C view shows, maximal excursion of aneurysm toward LA (left frame) lesser excursion toward RA (right frame).

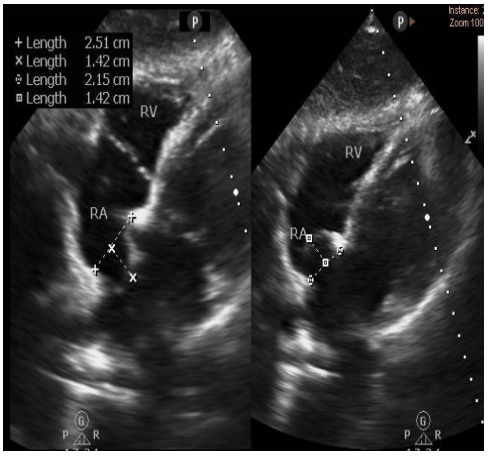

Figure 5: Type 5 ASA: Sub-costal four chamber view shows bidirectional and equidistance excursion of aneurysm in both atria

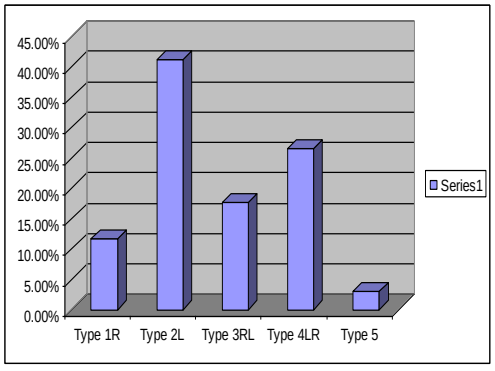

Figure 6: Clustered column with a 3 Dimensional effect chart shows percentage of different types of Isolated Atrial Septal Aneurysm.

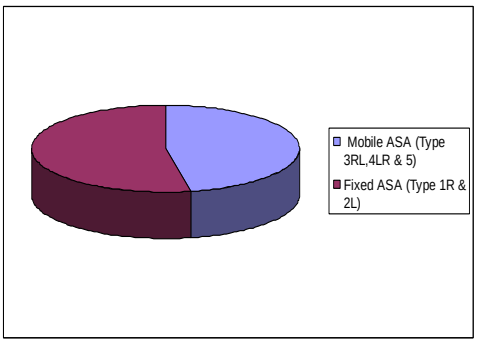

Figure 7: Pie with 3 Dimensional effect shows fixed type ASA in 52.94% and mobile ASA in 47.05%, in the present study.

We also evaluated a possible relationship between ASA morphology and type of migraine. Type 2 L and Type 4LR are significantly associated with occurrences of aura. Type 1 R and Type 3RL were more common with Group B. Isolated ASA is more common in females {21 (61.76%)}. Of these 21 female ASA patients: 15 patients (71.42%) are present in group "A" and 6 (28.57%) are found in group "B". Fixed type of ASA (52.94%) and bulging toward left atrium (69.69%) was common in the present study (Figure 7 & Table 3, 4).

Table 3: Mobile and Fixed atrial septal aneurysm in "A" and "B" group.

Mobile ASA [16 (47.05%)]		Fixed ASA [18 (52.94%)]	
Type 3 RL	6 (37.5%)	Type 1R	4 (22.22%)
Type 4 LR	9(56.25%)	Type 2 L	14(77.77%)
Type 5	1(6.25%)	----	----

Table 4: Pre-dominant excursion (Bulging) of atrial Septal aneurysm in both A and B group

Toward LA [23 (69.69%)]		Toward RA [10(30.30%)]	
Type 2 L	14 (60.86%)	Type 1 R	4 (40%)
Type 4LR	9 (39.13%)	Type 3 RL	6 (60%)

[Type 5 ASA (n =01) was excluded because this type do not have atrial predominance]

4. Discussion:

The first report on an atrial septal aneurysm (ASA) was published by Lang and Posselt in 1934 [21] since than several ASA cases and studies have been published in the literature. An aneurysm of the interatrial septum is an infrequent finding in adults. ASA formations can be secondary to interatrial pressure differences but may also be a primary malformation involving

the region of the fossa ovalis or the entire septum ; however, it has been also found in patients with normal atrial pressure [22], suggesting a primary (Congenital) malformation. Congenital malformation of the atrial septum probably contributes to development of ASA, as was suggested by Hanley PC and colleagues. ASA may be an isolated cardiac abnormality but is often found in association with other cardiac abnormalities, e.g. Cardiogenic embolic events and pulmonary venous, mitral valve or tricuspid valve obstruction, etc. It is also associated with congenital heart disease like ASD, VSD etc. In 1997 Alexander Olivares-Reyes et al [23], studied 205 patients with TTE and TEE and classified ASA in to five types and they added the letter "R" after the number if the septal bulging is toward the right atrium and the letter "L" if the bulging is toward the left atrium. They also added a second letter in ASAs which have excursion into both atria. In that case the first letter indicates the predominant direction of protrusion, and the letter in the second position indicates the lesser and opposite excursion. In the case where the aneurysm bulges throughout both atria in an equal or bidirectional fashion , this type is not followed by any letter and the number is used alone (type5). The Five types of ASA are as follows: (1) Type 1R : The ASA protrudes from the midline of the atrial septum to the right atrium throughout the cardiorespiratory cycle; (2) Type 2L : The ASA protrudes from the midline of the atrial septum to the left atrium throughout the cardiorespiratory cycle; (3) Type 3RL: The maximal excursion of the ASA is toward the right atrium with a lesser excursion toward the left atrium; (4) Type 4LR; The maximal excursion of the ASA is toward the left atrium with a lesser excursion toward the right atrium; and (5) Type 5: The ASA movement is bidirectional and equidistant to the right as well as to the left atrium during the cardiorespiratory cycle.

There is a female predominance in ASA in our study. Isolated ASA was found in 34 patients; of these 21 patients were female (61.76%) and 13 patients (38.23%) were male. Although some reports also show this tendency [24], [25], [26], other studies report no significant difference between genders. In fact some have reported a male predominance [27].The prevalence of PFO (37.5%) was significantly higher in adult female with migraine with aura as compare to migraine without aura patients (30%) in the present study.

The prevalence of ASA is significantly higher in the patients with migraine with aura compared with patients with migraine without aura and with control subjects .In our study all diagnosed atrial septal aneurysms were isolated without any other detectable abnormality; this could suggest a direct involvement of ASA in the genesis of aura.

An association between ASA and cryptogenic stroke has been reported [28], [29]. Several pathogenetic mechanisms concerning the relationship between ASA and cerebral ischemia have been hypothesized: clot formation near to the aneurysmatic surface which is often riddled with microscopic holes, paradoxical embolization through a coexistent PFO or atrial septal defect, association with other cardiac abnormality potentially responsible for embolism (e.g. Mitral valve prolapse) and rupture of generalized atrial septal aneurysm.

Echocardiographic differentiation between ASA-attached thrombi and artifacts created by mobile and bulging part of fossa ovalis may be difficult in some patients; a tangential scan through a mobile ASA may create the false impression of a thrombus. These difficulties in reliably differentiating between true thrombi and artifact may explain the differences in the incidence of thrombi attached to the ASA .Whether or not the echo densities that appear attached to an ASA are truly clots, the overall low incidence would suggest that an ASA on its own is unlikely to be a common site of thrombus formation. It should be noted; however TTE has a certain limit of resolution for thrombus detection. This resolution limit has not been defined and may be influenced by several factors, such as density of the thrombus and its relation to the surrounding blood and tissue. Thus this study does not exclude the possibility that small (micro) thrombi are attached to or at least generated in the region of ASA, subsequently causing cardiogenic embolism.

Migraine, particularly migraine with aura, has been suggested as a possible risk factor for cryptogenic stroke [30], [31], [32]. The high prevalence of ASA in patients with migraine with aura could further contribute to clarify the relationship between migraine and cryptogenic stroke.

5. Conclusions: we concluded the prevalence of an isolated atrial septal aneurysm in adults with migraine patients is high. Isolated ASA is more frequently detected and diagnosed now because of better cardiac ultrasound equipment and increased degree of suspicion for this entity. All types of ASA have their clinical significance and individual characteristic echocardiographic features .Isolated ASA is more prevalent in female with migraine with aura patients. Bulging towards the left atrium and fixed type were common in the present study.

Present study suggests a role of atrial septal aneurysm in the genesis of aura in patients with migraine. The limitations of our study were, less number of patients was included and this is a single center study, and findings may not be generalized to different populations and it require multicenter study

6. Abbreviations: ASA: Atrial septal aneurysm, ASD: Atrial septal defect, PFO: Patent foramen ovale, VSD: Ventricular septal defect, ECG: Electrocardiography, EEG: Electroencephalogram, TTE: Trans-Thoracic-Two Dimensional Echocardiography, TEE: Trans-Esophageal-Echocardiography, RA; Right atrium, LA; Left atrium, RV; Right ventricle.

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