Epidemiology and Clinical Study of Buerger's Disease

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Abstract

Thromboangiitis obliterans (TAO), also known as Buerger's disease or von Winiwarter-Buerger syndrome, is a chronic, inflammatory, thrombotic, nonatherosclerotic, segmental, obliterative, tobaccoassociated vasculopathy primarily involving infrapopliteal and infrabrachial medium-sized and small arteries of predominantly young male smokers, occurring prominently in young male smokers, predominantly affecting small and medium sized vessels and veins in the upper and lower extremities. The aetiology of TAO is unknown but there is a strong association with heavy tobacco use. This study was undertaken to study the mode of presentation of TAO, evaluation of the patient in order to assess the severity and effects of various modalities of treatment. It has a strong and positive association with smoking the cessation of which can bring about remission.

Keywords: Thromboangiitis Obliterans; Intermittent Claudication; Rest Pain; Peripheral Arterial Disease.

Introduction

Buerger's disease or TAO was first described by Leo Buerger in the beginning of 20th Century. TAO is found worldwide; it affects both sexes and all races, but with uneven gender and geographic distribution and probable ethnic predisposition. Buerger's view of the disease as being largely restricted to the Jewish race is nolonger valid. The only risk factor

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consistently reported Patients experience periods of acute exacerbation leading to critical limb ischemia associated with smoking, which may result in tissue loss and major amputations. Remissions follow abstinence from tobacco or can occur in the fifth to sixth decades of life. Cerebral, coronary, visceral, ophthalmic, and multisystem arterial involvements have also been described. A number of studies agree that tobacco use has a strong link to the pathogenesis and progression of TAO Indeed, the only fully effective therapy for Buerger's disease is complete and permanent discontinuation of smoking. Local wound care is also essential in patients with ischemic ulcers. Prostacyclin analogues, distal arterial revascularization, gene and stem cell-based therapies may help patients with severe limb ischemia. The cornerstone of therapy is the complete discontinuation of cigarette smoking or the use of tobacco in any form. Quitters will almost always avoid amputations, whereas 40% or more of patients who continue tobacco use will progress to one or more amputations. Lumbar sympathectomy has a role in relieving rest pain and healing of the ulcers. Surgical revascularization is usually not possible, because of the diffuse segmental involvement and distal nature of the disease. Till such time what is required of us interested in these studies is to be optimistic and opportunistic towards our efforts in searching out the aetiology and learn the modern trends in the management of patients keeping always in view that management is meant primarily to mitigate the sufferings of the victims and afford them the maximum comfort under the present state of our knowledge of this disease.

Objective of the Study

- 1. To know the epidemiological features of Buerger's disease in our patients.
- 2. To study the risk factors of the disease in our patients.

3. To assess the clinical features to diagnosis of the disease.

Methodology

Forty patients in the age group of 20-50 years who were smokers, presenting with symptoms of ischemia in limbs and were admitted our Hospital were taken up for study.

Duration of study - 6 months

Period of study - Dec 2016 to July 2017.

The method of the study consisted of taking a good clinical history in a chronological order as soon as the patient was admitted. A thorough clinical examination was carried out personally to find out and establish clinically first, the presence of vascular obstruction. Detailed vascular system examination was done as per the proforma provided and blood pressure measured to rule out hypertension. The degree of vascular inadequacy and extent of the spread of the disease was assessed clinically by noting the colour change, extent and spread of gangrene and absence of peripheral pulses in the affected limbs. This together with history of the patient

regarding the distribution and type of pain gave in a fairly good number of cases studied, an idea of the state of patients vascular condition. Risk factors, the presence of which formed basis for exclusion of the patient from study. Based on history, physical examination and investigation patients were either included or excluded from the study.

Inclusion Criteria

Following patients admitted our Hospital with symptoms of ischemia of upper and lower limbs were included in the study.

- 1. Age less than 50 years.
- 2. Onset before the age of 50 years.

Exclusion Criteria

Following patients admitted our Hospital with symptoms of ischemia of upper and lower limbs were excluded from the study.

- 1. Age more than 50 years.
- 2. Risks factors for atherosclerosis other than smoking.
- 3. Upper limb and suprapopliteal arterial occlusions.

Result

Table 1: Age distribution

Age in years	Number of patients	%
21-30	5	12.5
31-40	16	40
41-50	19	47.5
total	40	100

Table 2: Sex distribution

Sex	No of Patients	0/0
Male	40	100
Female	0	0
Total	40	100

Table 3: Religion distribution

Religion	No of patients percentage	%
Hindu	37	95
Muslim	03	7.5
Total	40	100

Table 4: Socio Economic status

SES	Number of patients	Percentage %
Lower	27	67.5
Middle	9	22
Higher	4	10
Higher Total	40	100

Table 5: Smoking distribution

Smoking History	Number of patients	0/0
Present	40	100
Heavy smokers	35	87.5
Moderate smokers	5	12.5

Table 6: Mode of presentations

Mode of presentation	Right	t (n=40)	Left	(n=40)	Tota	al (n=80)
-	No	%	No	0/0	No	%
IntermittentClaudication	24	60	20	50	44	55
Rest pain	19	47.5	22	55	41	51.5
Gangrene	4	10	5	12.5	9	11.25
Ulceration	4	10	8	20	12	15
Superficial thrombophlebitis	0	0	0	0	0	0
Raynaud'sphenomenon	0	0	0	0	0	0
Cyanosis of toes	0	0	0	0	0	0

Table 7: Distribution of gangrene, ulcer and superficial Thrombophelebitis

Local Examination	Number of Patients	(N=40) %
Gangrene	9	22.5
Ulceration	12	30
Superficial thrombophlebitis	0	0

Table 8: Incidence of upper and lower limb Involvement

Limb Involvement	Number of patients	(N=40)
Lower limb	14	100
Right	17	42.5
Left	10	25
Both	7	17.5
Upper limb	0	0
right	0	0
Left	0	0
Both UL and LL	0	0

 Table 9: Peripheral vessels involvement

Sl. No.	Peripheral Vessels	No. of Patients	Percentage
1	Dorsalispedis artery	25	62
2	Posterior tibial artery	27	67
3	Dorsalispedis and posterior tibial artery	40	100
4	Dorsalispedis, posterior tibial and popliteal artery	1	0.4
5	Radial and ulnar artery	0	0

Table 10: Doppler Scanning

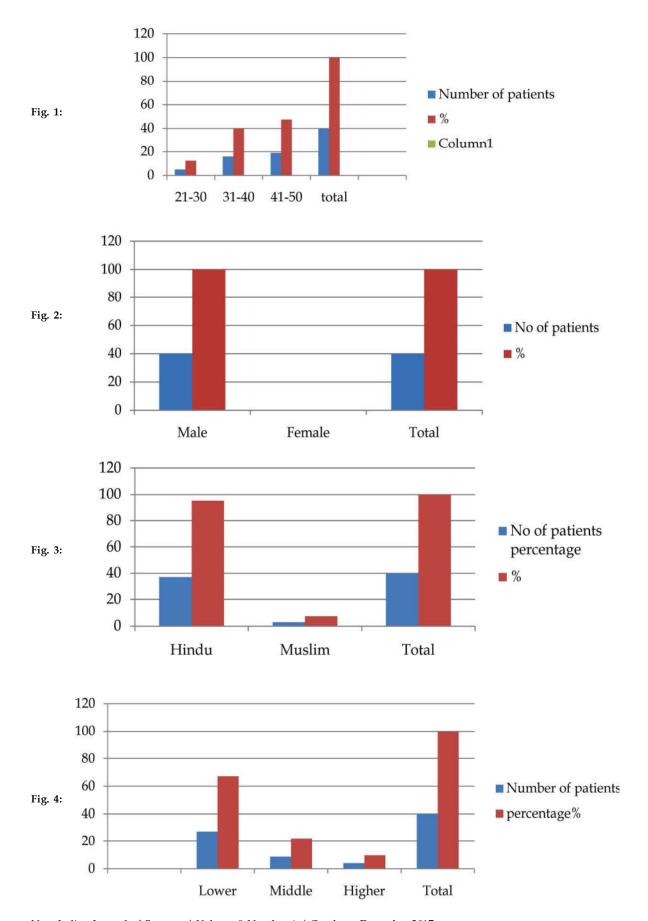
Doppler scanning	Number of patients	(N=40) %
Positive	16	40
Not done	24	60

Table 11: Modalities of Treatment

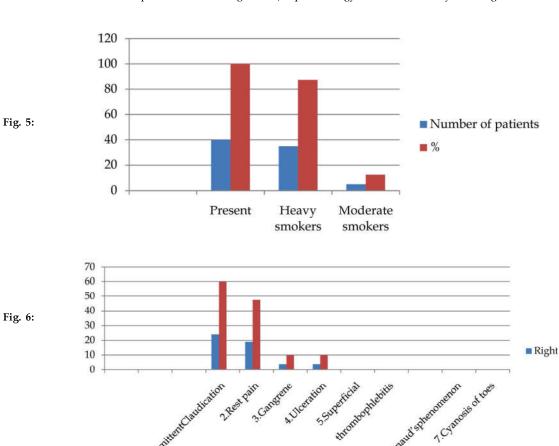
Treatment	Number of patients (n=40)	0/0
Conservative management	19	47.5
Lumbar sympathectomy	10	25
Amputation	6	15
Disarticulation	2	5

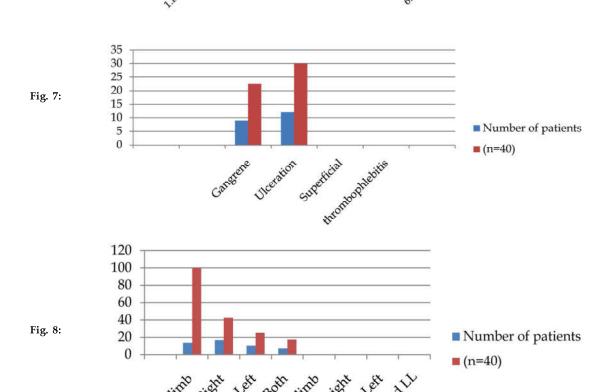
Table 12: Follow up

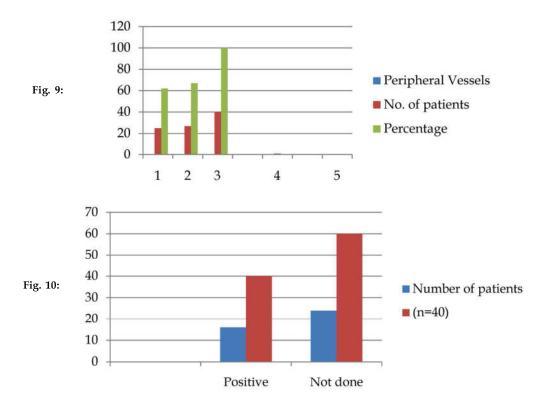
Follow up (n=40)	Number of patients	0/0
yes	34	85
no	06	15

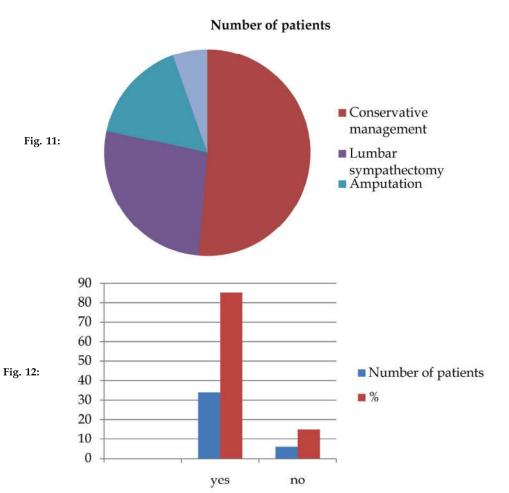


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Discussion

It can be appreciated from this study that this disease involves lower limbs. It affects young men. 40 patients were studied based on the clinical criteria. Among the 40 patients studied 40% of patients were diagnosed in the third decade and 47.5% cases were diagnosed after the age of 40 years. This is similar to the age incidence as reported by Lau H and Cheng in a study of 89 cases in Hong Kong. Our study included only males as the disease is rare in women and also because of the factthat women in India rarely smoke. History of familial cases of Buerger's disease were not seen in our study. Buerger had given age incidence of TAO between 20-30 years. His average being 32yrs and 5months. Homan's series (1936) lies between 20-40 years and Wright's (1948) between 40-55 yrs. In Mayo clinic series youngest was 17 years of age and oldest was 73 years. So it appears obvious that it is safe to make a diagnosis of TAO clinically in patients between 20-50 years of age, and with a strong radiological and pathological evidence after the age of 45 years. In our study, 27 patients (67.5%) were from low socio-economic status, 9 patients (22.5%) were from middle class and only 4 patient (10%) was from higher socioeconomic status. This clearly shows that there is predisposition of TAO in patients of lower socio-economic status.

Incidence of Involvement of Upper and Lower Limbs

In our series, all patients had involvement of lower extremities constituting 100% of all cases. No cases in our series with only upper limb involvement and involvement of both upper and lower extremities were present. Of the 40 patients presenting with involvement of lower limbs, 10 patients (25%) had involvement of left lower limb, 17 patients (42.5%) had involvement of right lower limb and 7 patients (17.5%) had bilateral lower limb involvement.

Smoking Distribution

The analysis of smoking history of the 40 patients studied, clearly shows how closely these patients were habituated to smoking. There were no nonsmokers in the series. Most of the patients in the series were heavy smokers, constituting 35 patients (87.5%) who smoked more than 20-25 beedies per day and 5 patients (12.5%) were moderate smokers who smoked between 10-20 beedies/day. All these patients smoked locally prepared rough beedies. No particular type of tobacco could be incriminated as different patients smoked different types of beedies. The interval

between smoking and onset of the disease in the present series varied from 5-25 years. The highest incidence was seen between 5-15 years. According to Hill et al, in their study, all the patients were cigarette smokers and patients who smoked more than 10 cigarettes per day had a much worse prognosis than those who smoked less than that.

Clinical Presentation

Out of the 40 cases studied, gangrene was present in 9 patients (22.5%). 10 patients had gangrene of one or more toes and other 5 patients had gangrene of the whole of forefoot. The mode of presentation was insidious in all the cases. In our study of 40 patients, all the patients had one or more signs of chronic ischemia. Out of 40 cases studied, ulceration was present in 12 patients (30%). Invariably the ulcers were seen at the tip of the toes, under surface or near the nail bed, due to pressure effects. Of the 15 patients presenting with gangrene, 6 patients 80 (40%) had a definite line of demarcation and other 9 patients (60%) did not have definite line of demarcation. In all 40 cases studied, there was evidence of impaired arterial pulsation on physical examination. The severity of symptoms also varied according to the site of arterial block. 40 patients (100%) had combined involvement of Dorsalis pedis and posterior tibial arteries and only 1 patient (0.4%) had involvement of all the three arteries i.e., dorsalis pedis, popliteal and posterior tibial. In the present study all the patients had infrapopliteal pulsation intact which is in accordance with the available literature on Buerger's disease.

Case Discussion

Aetiology

The aetiology of Buerger's disease remains unknown following causes have been described.

• Immunologically Mediated Injury to Smoking by Autoimmune Mechanisms

It has been suggested that an unidentified antigen possibly related to a constituent of tobacco smoke triggers immunologic damage to the arterial intima. Usually 20 or more cigarettes or beedies per day is required for disease to occur. Of note, most patients with TAO improve with cessation of smoking. Matsushita and associates, using urinary levels of cotinine, showed a very close relationship between active smoking and the aggravation of Buerger's disease. Several observations implicate an

immunologic phenomenon in the aetiology of Buerger's disease. In 1933, Harkavy suggested the possibility of hypersensitivity to tobacco antigens.

• Endothelial Dysfunction

Studies showed activation of endothelial cells associated with tumor necrosis factor- α secretion by tissue infiltrating mononuclear inflammatory cells and expression of intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin on endothelial cells in TAO patients.

• Hypercoagulable States

Recombinant A box (rAbox), the antagonist of HMGB1, improved the pathologic condition by inhibiting the release and injury of inflammatory mediators and improving the hypercoagulable state of blood.

Autonomic Overactivity

Sympathetic over activity causes segmental vasospasm which leads on to endothelial dysfunction. The cause of sympathetic over activity appears to be due to circulating levels of increased catecholamines released from adrenals in response to nicotine.

• Genetic Predisposition

The importance of a genetic predisposition to tobacco sensitivity is not well documented, although some data suggest that an association is present. Tashiro reported that only 1% of TAO cases in Japan consisted of members of the same family. However, genes of the major histocompatibility complex, particularly HLA-A9 and HLA-B5, have been linked to TAO in a study from Liverpool, England.

Hyperhomocysteinemia

Levels of homocysteine in circulation is elevated in patients with Buerger's disease.

Pathophysiology

Thromboangiitis obliterans is a vasculitis characterized by a highly cellular inflammatory thrombus with relative sparing of the vessel wall. Although acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein and commonly measured auto antibodies are typically normal, abnormalities in immunoreactivity are believed to drive the inflammatory process. Patients with thromboangiitis obliterans have been shown to

have increased cellular immunity to types I and III collagen compared with those who have atherosclerosis. In addition, hightiters of antiendothelial cell antibodies have been detected in patients with this disorder.

Pathogenesis: The relationship to cigarette smoking is one of the consistent aspects of this disorder. Most of the patients have hypersensitivity to intra dermally injected tobacco extracts.

Pathologic Stages of Buerger's Disease

In the acute phase, a panvasculitis within small and medium-sized (1-to 5-mm diameter) arteries and veins is observed. Primary features of acute-phase TAO are occlusive, highly cellular arterial thrombus; polymorphonuclear leukocytes with karyorrhexis; so-called micro abscesses around the periphery of the thrombus; one or more multinucleated giant cells; marked inflammation involving all layers of the vessel wall; intimal thickening; and neutrophilic infiltration of the entireneurovascular bundle. Multinucleated giant cells can be seen, but fibrinoid necrosis and granulomatous lesions are not observed.

Subacute phase in which there is progressive organization of the occlusive thrombus, with partial recanalization and disappearance of the microabscesses. Both immunoglobulins and complement factors are deposited in a linear manner along the elastic lamina, which is characteristic of the acute or subacute phase. An inflammatory response, including CD3+ pan-T cells, CD4+ T helperinducer cells, and CD20+ pan-B cells, to the internal elastic lamina of the affected vessels has been shown in detail. Infiltrating cells in acute and subacute lesions are more abundant than in chronic lesions. In addition, CD 68+ macrophages or S-100+ dendritic cells can be detected, especially in the intima, during the acute and subacute stages.

The **chronic-phase** or end-stage lesion is characterized by organization of the occlusive thrombus with extensive recanalization, prominent vascularization of the media, and perivascular fibrosis. In TAO, granulomas consisting of palisading epithelioid cells and giant cells may occur in arteries and in superficial and deep veins. Regardless of the pathologic stage, the internal elastic lamina and the architecture of the vascular walls are well preserved in TAO, in contrast to atherosclerosis and other types of systemic vasculitis. Sato and colleagues recently investigated the mechanism of vessel wall preservation and intact internal elastic lamina in Buerger's disease.

Clinical Features

TAO usually is manifested with distal extremity ischemia in a smoker before the age of 45 to 50 years. The median age at diagnosis is 34 years. Characteristically, distal extremity ischemia involves the feet, legs, hands, or arms as the disease progresses it may involve more proximal arteries85. The typical patient is one who is a heavy smoker and had started smoking at an early age. Following is the spectrum of presentation of disease.

1. Intermittent Claudication

Claudication, from the latin, claudicatio= to limp, indicates one of the best defined clinical entity in medicine. that is:

- Brought on by walking.
- Not present on taking the first step (unlike osteoarthrosis).
- Relieved by standing still
- The pain is always experienced in a functional muscle unit.
- It is a cramp like pain
- It is reproducibly precipitated by a consistent amount of exercise or walking.
- It is promptly relieved by stopping of walking / exercise.

Site of pain and corresponding level of obstruction in TAO.

Limb threatening ischemia occurs when resting blood flow is insufficient to meet the nutrient demand of non-exercising muscles.

The clinical manifestation of limb threatening ischemia include.

- Ischaemic RP
- Ulceration
- Gangrene
 - Ischemic Rest Pain

Following are the features of ischemic rest pain

Rest pain is experienced not in a muscle group but rather in foot, especially the toes and metatarsal heads.

- It is continuous and aching type of pain.
- Pain is worse at night.
- Pain gets aggravated by elevation of foot above level of heart.
- Pain is partially relieved by hanging the leg below level of heart.

It implies a reduction of blood flow in the extremity to a level below that required for normal resting tissue metabolism.

Aorto iliac obstruction Iliac obstruction Femoro popliteal obstruction Distal obstruction Claudication in both buttocks, thighs and calf Unilateral claudication in the thigh and calf Unilateral claudication in the calf Femoral and popliteal pulses palpable

If left untreated it almost invariably results in tissue necrosis. It is due to ischemic changes in the somatic nerves. It is known as cry of dying nerves.

2. Lower Extremity Occlusive Disease Classification

LE occlusive disease may range from exhibiting no symptoms to limb-threatening gangrene. There are two major classifications based on the clinical presentations.

3. Paraesthesia

When the muscle pain begins, the patient often feels numbness, pins and needles and other types of paraesthesia in the skin of foot. This is due to shunting of blood from skin to muscle.

4. Recurrent Thrombophlebitis

Painful inflammatory swellings along the course of vein, which usually present with spontaneous pain and cord like swellings in the limbs. It commonly occurs on foot, leg, arm and forearm.

Migratory superficial thrombophlebitis can also occur in other condition like

Polycythemia

Polyarteritis

Visceral malignancies (Pancreatic carcinoma).

The upper extremities may be involved and migratory superficial thrombophlebitis may be present in 16% of patients, thus indicating systemic inflammatory response.

5. Swelling and Oedema

The occurrence of swelling and oedema is unusual presenting symptom. It is not infrequently seen in the latter phase of the disease. The causes of its occurrence are mainly due to capillary stagnation, persistent dependency of the limbs, which the patient deliberately seeks to get some comfort and relief from RP, sepsis and lymphangitis secondary to infection.

6. Chronic Sepsis

Impaired blood supply and chronic inanition of the tissues of the affected limbs, undermine the tissue resistance to bacterial invasion and predispose to infections.

Minor or trivial trauma like careless pairing of the nails, thorn pricks, etc precipitate.

Diagnosis

History taking and physical examination are usually sufficient to make the diagnosis of Buerger's disease, but additional diagnostic procedures are required to evaluate the degree of ischemia objectively and to select the most appropriate therapy.

The traditional diagnosis of TAO is based on Shionoya's criteria, with all five elements required:

- 1. Smoking history,
- 2. Onset before the age of 50 years,
- 3. Infrapopliteal arterial occlusive lesions,
- 4. Either upper limb involvement or phlebitis migrans, and
- 5. Absence of atherosclerotic risk factors other than smoking.

Role of Investigations

Following is the role of investigations in TAO

- To rule out atherosclerotic risk factors
- Quantification of severity and level of block
- Diagnosis of disease in doubtful cases

FBS, serum lipid profile and coagulation profile are done to rule out atherosclerotic risk factors. Cardiac size and coronary state as studied by X-ray and ECG rule out atherosclerosis. Absence of cardiac manifestation like angina, absence of hypertension and absence of calcification of the arterial wall on plain X-ray of the limbs rules out possibility of atherosclerotic involvement.

Non-Invasive Vascular Testing

1. Pressure Measurements

Technique: The blood pressure cuff is placed above the ankle and inflation of the cuff is done until the doppler signal disappears.

Indication

- Patients presenting with features of ischemia.
 - Ankle-Brachial Index

There is increasing interest in the use of the ankle brachial index (ABI) to evaluate patients at risk for cardiovascular events. An ABI <0.9 correlates with increased risk of myocardial infarction and indicates significant, although perhaps asymptomatic, underlying peripheral vascular disease.

The ankle pressure is determined by placing a BP cuff above the ankle and measuring the return to flow of the posterior tibial and dorsalis pedis arteries using a pencil doppler probe over each artery. The ratio of the systolic pressure in each vessel divided by the highest arm systolic pressure can be used to express the ABI in both the posterior tibial and dorsalis pedis arteries. Normal is more than 1. Patients with claudication typically have an ABI in the 0.5 to 0.7 range, and those with rest pain are in the 0.3 to 0.5 range. Those with gangrene have an ABI of <0.3.

• Segmental Limb Pressures

By placing serial BP cuffs down the LE and then measuring the pressure with a Doppler probe as flow returns to the artery below the cuff, it is possible to determine segmental pressures down the leg. These data can then be used to inferior to level of the occlusion. The systolic pressure at each level is expressed as a ratio, with the highest systolic pressure in the upper extremities as the denominator. Normal segmental pressures commonly show high thigh pressures 20 mmHg or greater in comparison to the brachial artery pressures.

• Pulse Volume Recording

In patients with non-compressible vessels, segmental plethysmography can be used to determine underlying arterial occlusive disease. Cuffs placed at different levels on the leg detect changes in leg volume and produce a pulse volume recording (PVR) when connected to a plethysmograph. To obtain accurate PVR waveforms the cuff is inflated to 60 to 65 mmHg

to detect volume changes without causing arterial occlusion. Pulse volume tracings are suggestive of proximal disease if the upstroke of the pulse is not brisk, the peak of the wave tracing is rounded, and there is disappearance of the dicrotic notch.

2. Doppler

Principle of Doppler: A continuous wave ultrasound signal is beamed at an artery and reflected beam picked up by a receiver. The changes of frequency in the reflected beam, as compared with transmitted beam, are due to the 'Doppler Shift', resulting from passage of the beam through moving blood. The frequency change is converted into visual or audio signal.

Indications

Before arterial reconstruction to provide baseline for future comparison.

Before angiography to guide the angiographer.

In patients who are not operative candidates, the doppler study allows following progression of disease.

Pulse Wave Velocity Analysis (PWV)

The PWV measures the velocity of conduction of pulse wave across the vessel wall, and as the wall stiffens due to calcification the PWV increases in value. The typical PWV analysis of normal artery is 'Triphasic'. It consists of

- a. Strong forward component of blood flow during systole.
- b. Short reversal of blood flow during early diastole.
- c. Return to forward flow of lower amplitude during later diastole.

Following are normal peak velocity measurements.

Common femoral - 100 cm/sec

Popliteal artery - 70 cm/sec

Tibeoperoneal - 40.50 cm/sec

3. Duplex Scanning

Duplex Implies two Forms of USG

B-mode which is typically used to create two dimensional gray-scale anatomic image

Doppler USG

The B-mode imaging is used to guide placement of

Doppler sampling volume at different locations and the resulting, frequency or velocity shift can be used to grade severity of obstructive lesions.

Duplex scanning has become the first line tool for imaging lower extremity bypass grafts. Duplex arterial mapping of the lower extremity also is being used increasingly as an alternative to angiography.

Duplex scanning with spectral waveform analysis has several distinct advantages over the indirect noninvasive tests for PAD, following are the advantages:

- Lesions can be accurately localized
- Lesions can be detected at multiple level in same limb
- Stenosis can be classified according to degree of severity
- Minor lesions can be recognized

Invasive Vascular Testing

Angiography: Digital subtraction angiography plays an important role in both supporting the diagnosis of TAO and ruling out other causes of ischemia.

Arteriographic findings in TAO may be suggestive but not pathognomonic. Thus, this method is not a 'gold standard' for diagnosis. Segmental occlusive lesions (diseased arteries interspersed with normal appearing arteries), more severe disease distally, involvement of digital arteries, normal proximal arteries without evidence of atherosclerosis and collateralization around areas of occlusion with corkscrew-shaped collaterals (Martorell's sign, also described as 'tree root' or 'spider leg' collaterals) are the common features of TAO.

Management

The mainstays for treatment of Buerger's disease include first and foremost smoking cessation, followed by improving arterial flow to the limb, alleviating ischemic rest pain, treating concomitant infection and thrombophlebitis, and improving local wound healing. Summarizes the various treatment options for TAO. Effective treatment must be individualized and is often based on the specific clinical manifestations.

Conclusion

 Thromboangiitis obliterans is a peripheral vascular disease which usually affects young males, involves predominantly the lower limbs than upper limbs.

- This was a prospective study conducted our hospital in 40 cases of Thromboangiitis Obliterans admitted from dec 2016 to july 2017.
- Available literature of Buerger's disease reviewed.
- The age of onset is in the third decade
- Males are commonly involved / all the involved patients were males.
- No familial incidence was seen in our study.
- Lower socio-economic strata people are commonly involved with Buerger's disease
- All patients were smokers and patients who smoked more than 20 beedis per day had more severe disease than those who smoked less.
- Lower limb is commonly involved.
- Resting pain in the limb with intermittent claudication was the predominant symptom in majority of patients.
- Medium and small calibre vessels of the lower limb are commonly involved in Buerger's disease.

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