Introduction

Systemic sclerosis (SSc) or scleroderma (Greek, skleros, hard and derma, skin) is characterized by fibrosis and vascular obliteration in the skin, gastrointestinal tract, lungs, heart, and kidneys. The onset and course of the disease is heterogeneous ***(Prado, 2002)***.

Scleroderma can be classified according to the extent of skin and visceral involvement as either a diffuse or limited form ***(Prado, 2002).***

Neurological involvement in SSc is not as common as in systemic lupus erythematosus, but in recent studies it is demonstrated, however, that neurological involvement in SS is more frequent than what had been assumed. ***Campello-Morer (2003)*** did clinical neurological exploration in 26 patients with definitive SS in order to determine the prevalence of central neurological pathology and of peripheral neuropathy, to define its characteristics, and to investigate possible associations with clinical parameters and with autoimmunity. They found that seven patients (26.9%) showed involvement of the CNS, being the headache and the neuropsychiatric manifestations the most common conditions followed by peripheral neuropathy ***(Campello-Morer, 2003).***

A high prevalence of depressive symptoms has been described in systemic sclerosis (SSc), ***Beretta (2006)*** tried to determine the prevalence of depressive symptoms in one-hundred-eleven Italian patients with SSc to clarify their cause. They

concluded mild to severe depressive symptoms are common in SSc patients especially in those with a worse perception of disease severity, these patients should be carefully monitored and a psychological assistance counseled ***(Beretta, 2006)***.

Peripheral nervous system (PNS) involvement in systemic sclerosis (SSc) using electrophysiological studies showed patients with sensory-motor axonal polyneuropathy, patients with distal multiple mononeuropathy (upper limbs) and patients with proximal myopathy. Patients with polyneuropathy were in atrophic stage of disease with duration >5 years ***(Lori, 1996).***

Manneschi (2005) found that Damage of cutaneous peripheral nervous system evolves differently according to the disease phase and subset of systemic sclerosis and thus, an early therapeutic approach can be useful to reduce the progression of PNS and skin damage in SSc patients.

TIA or stroke are uncommon complications of PSS and have been associated with renal failure and severe hypertension**.** however some cases of ischemic stroke without hypertension or renal failure have been recorded ***(Das, 2002).*** Vascular and dysimmune mechanisms may produce cerebral ischemia in absence of systemic atherosclerosis or any vascular risk factors ***(Chung, 1995)***.

Aim of the Work

The aim of this work is to study the neurological and neuropsychiatric manifestations in patients with systemic sclerosis and its correlation to disease activity and other organ involvement.

Systemic Sclerosis

Systemic sclerosis (SSc) is a chronic multisystem autoimmune disease that is highly heterogeneous and has multiple overlapping and poorly defined clinical subsets. The two widely recognized subsets of SSc are limited cutaneous and diffuse cutaneous SSc with divergent patterns of organ involvement, tempo, autoantibody profiles, and survival. The prominent features of the disease reflect the characteristic pathophysiologic triad of autoimmunity and inflammation, vascular damage, and fibrosis ***(Varga, 2008).***

Historical Background:

The first detailed description of a scleroderma-like disease was published by Curzio in Naples in 1753. The patient, a young women suffered from excessive tension and hardness of the skin. Nearly 100 years later, in 1847 Gintrac introduced organ involved. The extensive involvement of internal organs has only been realized in the second half of the 20th century ***(Haustein, 2002).***

Epidemiology: The true incidence is underestimated since early features are overlooked is between 2-6 and 20 to 28 per million 1 year.

Sex: The overall female/male ratio was reported as 3:1, however, this ratio is larger in Great Britain (6:1) and in the USA (8:1) ***(Haustein, 2002).***

Race: The prevalence of SSc is reported to be between 13 to 105 and 13 to 140 per million in North America, Australia and Europe, respectively ***(Haustein, 2002).***

Age: The average onset of SSc occurs between 40 and 50 years, but in women it is in the late childbearing years between 30 and 39 years. Less than 10% of patients develop SSc before the age of 20 ***(Haustein, 2002).***

Mortality:

Systemic sclerosis has the highest case-fatality among the connective tissue diseases, with a 10-year survival of 55%. However, survival during the past decade has shown improvement ***(Varga, 2008).***

Pathogenesis:

The pathogenesis of SSc encompasses vascular, immunological and fibrotic processes, which contribute to clinical manifestations and morbidity and must be addressed in the treatment plan ***(Varga, 2008).***

Inflammation: It is now generally accepted that vascular injury (possibly caused by virus, autoantibody, or oxidation products) is a very early event. The resulting endothelial cell activation and apoptosis lead to inflammation and activation of T-cells, B-cells, and macrophages. There is evidence for involvement of both innate

and adaptive arms of the immune response.Lesional T-cells show Th2 polarization suggestive of an antigen-driven response. Recent studies also implicate the Th17 subset of T-cell cytokines, such as IL-17 and IL-23, in the development of fibrosis ***(Varga, 2008).***

Fibrosis: Cytokines and growth factors, such as TGF-β, platelet-derived growth factor (PDGF) and endothelin-1 (ET-1), secreted in the skin and lungs activate resident fibroblasts, promoting accumulation of collagen, proteo-glycans, fibronectin, tenascin, and elastin. Furthermore, TGF-β, induces the differentiation of fibroblast into smooth muscle cell-like myofibroblasts in situ. Because myofibroblasts are also capable of entrancing the stiffness of the extracellular matrix (ECM), elaborating matrix molecules and profibrotic cytokines, and are relatively resistant to apoptosis, their accumulation and persistence within lesional tissue contributes to the progression of the fibrosis. The fibroblast population within lesion tissue is expanded by the arrival of bone marrow-derived mesenchymal progenitor cells, called fibrocyte, which then further contribute to connective tissue accumulation. The signals that instruct the bone marrow to mobilize progenitor cells and govern their homing and engraftment in lesional tissue remain unknown. A recent report demonstrated that SSc patients have circulating antibodies directed against the PDGF receptor that are capable of triggering activation of fibroblasts ***(Baroni, 2006)*** once collagen is secreted into the extracellular space, it undergoes cross-linking and maturation, resulting in a highly stable matrix that

accounts for the stiffness of fibrotic skin and other tissue. The stiff matrix may itself serve as a strong stimulus for intergrin-mediated TGF-β activation and increasing fibrosis ***(Varga, 2008).***

TGF-β: In normal fibroblasts, TGF-β induces a gene activation signature that is virtually identical to the phenotype of SSc fibroblasts. Furthermore, animal models provide strong support for the critical pathogenetic role of TGF-β, in the fibrotic process in the skin and lungs ***(Daniels, 2004).***

Vasculopathy: Vascular damage is prominent in the small and medium-sized vessels of the digits, lungs, heart and gastrointestinal tract changes progress through three distinct phases: (1) endothelial cell activation, with increased production of ET-1 and decreased prostacyclin release, causing functional changes with initially reversible vasoconstriction; (2) upregulation of adhesion molecules; and (3) generation of reactive oxygen species vascular wall remodeling follows with intimal proliferation, medial hypertrophy, and adventitial fibrosis; ultimately, platelet aggregation occurs and in situ thrombosis. The late vascular lesions are indistinguishable from the obliterative vasculopathy seen in organ transplant-associated allograft vasculopathy ***(Hinchcliff, 2007).***

Patients with long-standing SSc demonstrate vascular rarefaction i.e. paucity of small blood vessels, despite high levels of

vascular endothelial growth factor (VEGF) and other angiogenic factor ***(Fleming, 2008).***

Progressive obliteration of blood vessels results in tissue hypoxia which is itself a potent stimulus for production of TGF-β, and fibroblast activation. Further enhancing the fibrotic process ***(Varga, 2008).***

Etiology:

Genetic factors: The influence of genetics in SSc has been investigated although 1.6% of patients have a first degree relative with SSc (relative risk equals 13). Scanning the entire genome in SSc has identified informative single nucleotide polymorphism (SNPs), particular alleles in the genes for transforming growth factor-B (TGF-β), monocytes chemo-attractant protein-1 (MCP-1), IL-1α, tumor necrosis factor, allograft inflammatory protein-1 (AIF-1), and angiotensin converting enzyme (ACE) have been linked to disease susceptibility ***(Fonseca, 2007).***

Furthermore, distinct HLA allele associations with disease or with a particular autoantibody response have been reported ***(Varga, 2008).***

Environmental: Environmental factors induce SSc-like disease, several reports describe chemical compounds within our environment and their ability to induce SSc-like disease upon exposure which can be distinguished from SSc by the following. (i)

Type of skin manifestation in particular acrosclerosis, circumscribed and generalized morphea, fibrotic nodules, joint contracture. (ii) Visceral involvement due to toxic damage of the liver, kidneys, nervous system and muscle. (iii) Laboratory finding of partial thrombocytopenia and absence of autoantibodies, and reversibility of the disease after discontinuation of the exposure ***(Haustein, 2002).***

Chlorinated hydrocarbons may induce systemic diseases, but aromatic hydrocarbons are associated with local fibrosis restricted to the areas of direct contact. Tryptophan can trigger an eosinophilic fasciitis similar to Shulman syndrome or the eosinophilic myalagia syndrome ***(Haustein, 2002).***

In contrast to other environmental substances, silica is able to induce a form of SSc-like disease. However, the long exposure times needed for the onset of silica induced SSc also it will depend on the individual genetic background ***(Haustein, 2002).***

Viral: Cytomegalovirus (CMV) specific antibodies are elevated in some SSc patients. CMV infection in rodents can induce vascular lesions reminiscent of SSc vasculopathy ***(Varga, 2008).***

The American College of Rheumatologie: has defined criteria (Arthritis Rheum., 1980).

Major criteria: * Proximal diffuse sclerosis
Minor criteria: * Sclerodactly
* Digital pitting scars

* Bibasilar pulmonary fibrosis

The patients should fulfill the major criterion or two of three minor criteria.

Classification:

The most common subsets are limited cutaneous (approximately 60% of patients with systemic sclerosis) and diffuse cutaneous (approximately 35% of patients with SSc). The limited cutaneous subset is diagnosed when skin thickening is limited to areas distal to the elbows and knees.

CREST (Calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactly, telangectasia) syndrome is a variant of limited cutaneous SSc ***(Hinchcliff, 2008).***

Localized form of scleroderma as linear scleroderma and morphea primarily affect children and not associated with Raynaud's phenomenon or significant internal organ manifestations.

Table (1): Distinguishing clinical features of limited and diffuse cutaneous systemic sclerosis ***(Hinchcliff, 2008).***

Features	Limited cutaenous	Diffuse cutaneous
Skin fibrosis	Areas distal to the elbows and knees; may affect the face	Areas proximal or distal to the elbows and knees; may affect the face

Typical form of lung involvement	Pulmonary arterial hypertension	Interstitial lung disease
Characteristic visceral organ involvement physical examination findings	Severe gastroesophageal reflux disease and Raynaud phenomenon Telangiectasia, calcinosis cutis, sclerodactyly, digital ischemic complications	Scleroderma renal crisis Tendon friction rubs, pigment changes

Clinical Presentation:

A systemic sclerosis diagnosis is based on clinical findings, which have substantial heterogeneity and varying manifestations.

1-Skin: The degree of skin thickening depends on the subtype and duration of disease. Early in the disease, diffuse swelling of the fingers and hands may preceded skin thickening. Other early dermatologic changes include shiny skin or pigment changes. As the skin thickens on the fingers (sclerodactly), hands and forearms (limited cutaneous SSc), or trunk (diffuse cutaneous SSc), the SSc diagnosis becomes increasingly apparent ***(Hinchcliff, 2008).***

Several surveys have investigated the prevalence of sicca syndrome in patients with scleroderma, Xerostomia was present in 70% of the patients and was associated with increased frequency of dental caries ***(Shah, 2008).***

Other cutaneous manifestations include hair loss on involved skin; telangiectasia on the face, buccal mucosa, chests, and hands;

and calcinosis cutis. With disease progression ulceration over joints and flexion contractures of the fingers, wrists, and elbows may occur ***(Hinchcliff, 2008).***

Raynaud's phenomenon: Cold induced Raynaud phenomenon is the most common manifestation of SSc, occurring in more than 95% of patients. Patient's fingers may change from white (vasospasm) to blue-purple (ischemia) to red (hypermia); this is precipitate by exposure to cold temperature or emotional stress, primary Raynaud phenomenon typically occurs in female adolescents, and is not associate with ischemic complications. In contrast, secondary Raynaud phenomenon tends to occur later in life and often leads to tissue damage. Physical findings of secondary Raynaud phenomenon include cyanosis and signs of ischemic damage to the fingers, such as digital pitting, visible capillaries on the nail bed, ischemic ulcerations, and pterygium inversus unguis (i.e. distal nail bed adherence to the ventral surface of the nail plate) ***(Hinchcliff, 2008).***

2-Gastrointestinal tract:

Gut involvement is one major cause of serious morbidity, and next to the skin, the gastrointestinal tract is the most commonly involved organ ***(Sjolund, 2005).***

Esophageal involvement is frequent in SSc occurring as 50% to 90% of patients characterized by low pressure in the lower oesphageal sphincter (LES) and dysfunction of smooth muscle

motor activity and predisposes to prolonged GERD (gastroesophageal reflux disease) ***(Maries, 2001)***

It is still recognized to be associated with high morbidity in SSc patients as leads to (a) in ability to ingest sufficient calories, resulting in weight loss and malnutrition and electrolyte disturbances, and (b) "Barrett's esophagus" with its accompanying potential for adeno-carcinoma ***(Marie, 2001).***

Recently, many investigators have reported that GERD may be one of the initiating factors of respiratory disorders. They have implicated microaspirations of gastric content into the lungs ***(Maries, 2001).***

In the small intestine motility disturbances leads to stasis, followed by bacterial overgrowth, or decreased permeability as a result of intestinal fibrosis may cause streatorrhoea and malabsorption. Although the pathogenesis is not fully understood, it was suggested that the disturbed motility follows a two-stage process: an initial neuropathic disorders caused by the involvement of the enteric nervous system and a later stage of muscle failure ***(Sjolund, 2005).***

Gastric involvement occurs in as high as 10-75% of SSc patients it is sill recognized as associated with high morbidity as gastroparesis may result in the following: (i) inability to ingest sufficient calories leading to malnutrition and (ii) gastro-esophageal

reflux exacerbation. Furthermore, gastric impairment may result in gastric bleeding related to antral vascular ectasia ***(Marie, 2006).***

Various clinical presentations may reveal watermelon stomach more commonly recurrent anaemia related to occult gastrointestinal bleeding (90.9% of cases) ***(Shibekawa, 2007).***

The endoscpic appearances are characterized by (I) typical "watermelon stomach" with prominent, flat or rased erythematous stripes radiating in a spoke-like fashion from the antrum to the pylorus (II) "honey comb stomach" vascular ectasia appear like a coalescence of many round angiodysplastic lesions in the antrum ***(Marie, 2008).***

Lower gastrointestinal symptoms are frequently under reported by patients with SSc. Diarrhea, constipation, or fecal incontinence is commonly present in this patient population and represents an important cause of deterioration in quality of life. Pathogenic mechanisms responsible for these symptoms are still unclear, although some evidence supports neural disruption preceding smooth muscle dysfunction and subsequent fibrosis ***(Heyt, 2004).***

3-Renal involvement:

Kidney involvement in systemic sclerosis (SSc) was first described in 1863. The denomination of scleroderma renal crisis (SRC) was first proposed in 1952 by Moore and Sheehan, who first described the typical histopathological lesion. SRC is an infrequent

complication of SSc that presents as new-onset accelerated-phase hypertension and/or rapidly deteriorating renal function, frequently accompanied by signs of micro-angiopathic hemolysis ***(Steen, 2003).***

Pathogenesis: The pathogenesis of SRC is incompletely understood. The typical vascular "onion bulb" lesion observed in SRC is the consequence of a proliferation of the vascular intima, which leads to a narrowing of the vessel lumen and reduced blood flow ***(Charles, 2006).***

Other mechanisms, such as vascular hyperreactivity, can take place, and Cannon in1974, reported a "renal Raynaud's phenomenon" responsible for a decreased renal perfusion mainly in cortical blood flow," and some authorsobserved an increased frequency of SRC during winter ***(Teixeira, 2007).***

Activation of the renin-angiotensin-aldosterone system seems to play an important role in the pathophysiology of SRC. A number of substances (e.g., cocaine) and drugs, including cyclosporine and corticosteroids have been implicated as precipitants of SRC ***(Teixeira, 2007).***

Clinical features: SRC occurs roughly in 4-6% of SSc patients, predominantly in those presenting with diffuse SSC and less than 2% in patients with limited cutaneous SSc (lcSSc) ***(Walker, 2007)***.