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DR. D. Y. PATIL COLLEGE OF PHARMACY

Happy World Pharmacist Day

THEME: "PHARMACY STRENGTHENING HEALTH SYSTEM"

TECH PHARMA

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DR. DY PATIL COLLEGE OF PHARMACY, AKURDI, PUNE

TABLE OF CONTENTS

PARAPSORIASIS

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PARAPSORIASIS

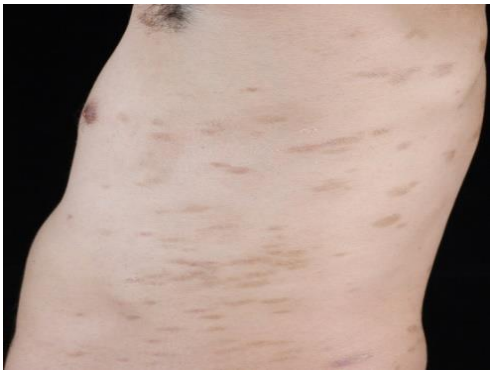
Parapsoriasis is an uncommon seditious skin complaint characterized by habitual patches that may be resistant to remedy. The word" parapsoriasis" was formed in 1902. It was primarily introduced and classified 120 times agone, and the original bracket incorporated parapsoriasis and pityriasis lichenoides under the marquee term parapsoriasis. tumours can develop from parapsoriasis. For illustration, it can develop into cutaneous T- cell carcinoma.

Introduction:

Parapsoriasis is a group of uncommon but not rare diseases, characterized by the patient, scaled, seditious eruptions. The current, generally accepted bracket includes three realities large shrine parapsoriasis [LPP], small shrine parapsoriasis [SPP], and pityriasis lichenoides. [1]

Parapsoriasis is an analogous appearing complaint to psoriasis. Both skin conditions partake symptoms like pillars, which are scaled patches on the skin, and rashes. Parapsoriasis is a term chased by Brocq in 1902, as a central link of his grand design encompassing all seditious dermatoses, to a group of conditions characterized by common features similar as unknown etiology, regularity, failure to respond to remedy, and lack of symptoms, particularly of pruritus. [1] Large shrine parapsoriasis is a complaint of middle-aged and aged people, with a peak prevalence in the fifth decade, with slight manly transcendence and no ethnical and geographical partiality. [1]

Clinically, LPP lesions are round or irregularly shaped asymptomatic or mildly pruritic patches or veritably thin pillars, with utmost lesions bigger than 5 cm in the periphery, and with fine wrinkles and skimp scales; telangiectasia and mottled saturation may also be observed. They're set up substantially on the' bathing box' and flexural areas, and on extremities and upper box, especially guts in women. [1] On histological examination, one observes an interface insinuate, and in the more advanced lesions, definite epidermotropism. [1]



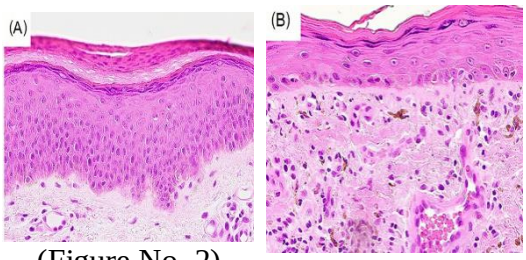
(Figure No. 1)

Parapsoriasis vs. Psoriasis

The name parapsoriasis comes from the similarity to psoriasis, as both diseases beget scaled pillars on the skin.

A crucial difference between the two diseases is that shrine coming from parapsoriasis is generally thinner than shrine from utmost typical forms of psoriasis. Treatment is frequently the same or analogous for both diseases. latterly, in 1926, removed pityriasis lichenoides from the parapsoriasis group, which was extensively accepted. utmost croakers agreed to reclassify parapsoriasis as a separate reality, which was proved in the literature [2].

After decades, the original bracket of parapsoriasis came less popular, and utmost dermatologists, currently, generally consider parapsoriasis as a single complaint with two subtypes SPP and LPP Fig No 1 still, confusion with the title of these conditions constantly occurs, not only with the nebulosity or variety of names but also with the language restatement.



(Figure No. 2)

For illustration, "parapsoriasis en pillars" was first established by a French croaker and the word "shrine" in French means "patch " in English. Accordingly, some croakers might have misinterpreted clinical appearance. likewise, the term "parapsoriasis en pillars" was interchangeably used for different conditions, either SPP or LPP, in previous studies. Another confusion is the lapping languages between parapsoriasis and mycosis fungoides [MF], such as parapsoriasis lichenoid's, retiform parapsoriasis, and parapsoriasis variegate. Some of these terms were used by experts to identify MF and continue to be used by some experts in the present day [2, 4, 5].

Parapsoriasis	Original Classification			
Entities	Parapsoriasis (Parapsoriasis en plaques)		Pityriasis lichenoides	
Subtypes	Large plaque parapsoriasis (LPP)	Small plaque parapsoriasis (SPP)	Pityriasis lichenoides et varioliformis acuta (PLEVA)	Pityriasis lichenoides chronica (PLC)
Variants	Poikilodermatous, retiform	Digitate dermatosis		
Parapsoriasis	Current Classification			

(Figure No. 3)

Clinical Characteristics

Parapsoriasis

Parapsoriasis is an uncommon, habitual papulosquamous dermatosis of unknown etiology. It occurs worldwide and most generally affects middle-aged or aged grown-ups, with a manly transcendence [6]. Utmost cases are asymptomatic or mildly pruritic but generally respond inadequately to treatments.

SPP

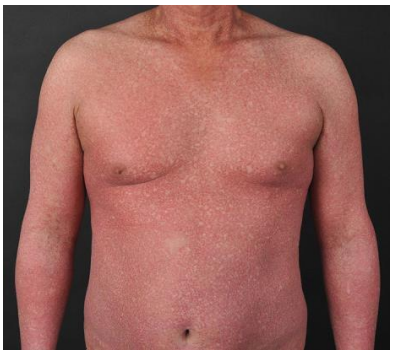
Former names habitual superficial dermatitis, parapsoriasis guttate, benign type, leopard-spot parapsoriasis, parapsoriasis en pillars, small shrine type/ simple separate type/benign types. SPP generally appears with round-to-round erythematous, unheroic, or brown macules and patches with fine scales. utmost lesions are lower than 5 cm in the periphery and generally involve the box and proximal extremities. SPP infrequently progresses.

"Digitate dermatosis" is a distinctive variant of SPP first reported by Hu and Winkelmann in 1973 [7], presenting with stretched, cutlet- suchlike patches located on the sides in a resemblant pattern [Fig. 2]. The long axis of skin lesions may be larger than 5 cm. The term "Xanthoerythrodermia perstans" has been used to link cases with unheroic skin lesions [2].

LPP

Former names atrophic parapsoriasis, poikilodermatous parapsoriasis, parapsoriasis en pillars, large shrine type/ atrophic type, parapsoriasis en grandes pillars simples, parapsoriasis en grandes pillars poikilodermiques, lichenoid stage of mycosis fungoides, poikilodermic mycosis fungoides, prereticulotic dermatitis, prereticulotic poikiloderma, parapsoriasis en pillars, poikiloderma vascular atrophicans, parapsoriasis lichenoides.

LPP is characterized by ill-defined, erythematous to brown patches or thin pillars with fine scales. A wrinkling skin face may be apparent. utmost lesions are irregular in shape and lesser than 5 cm in the periphery. The partiality spots are the box, flexural areas, shanks, buttocks, and guts. Skin atrophy, telangiectasia, and mottled hyperpigmentation are sometimes appreciated. The skin lesions composed of this trio are called poikiloderma or poikiloderma vascular atrophicans. Retiform parapsoriasis [parapsoriasis variegata, parapsoriasis lichenoides] is a veritably rare LPP variant characterized by wide reticulated skin lesions with frequent atrophic and scaled macules [2, 3]. Some experts considered this variant as poikilodermatous MF [8, 9].



(Figure No. 4)

Immunohistochemical staining reveals CD4 T cells in utmost insinuating lymphocytes with a minor population of CD8 T cells. The CD4CD8 rate is generally normal or mildly elevated. The reactive T cells express CD2, CD3, and CD5. Loss of CD7 expression may be observed [10, 11]

Histopathology

The histopathologic findings of both subtypes of parapsoriasis are nondiagnostic and can mimic colorful skin conditions, ranging from seditious dermatoses to cutaneous T- cell carcinoma [CTCL].

SPP shows mild acanthosis with parakeratosis, spongiosis, and meager superficial perivascular lymphohistiocytic insinuate. Confluent direct parakeratosis with tube collection over handbasket-weave keratin is a characteristic finding, Histologically, LPP may be identical to SPP. In addition, LPP may show further epidermal atrophy, patchy lichenoid lymphohistiocytic insinuate, and rudimentary vacuolization with melanin incontinence.

Association with Lymphoma

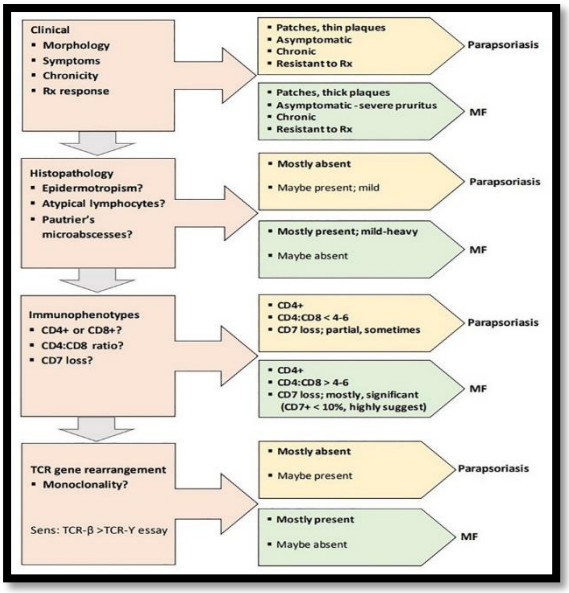
"The risk of progression to lymphoma is minimal in SPP, but it is dramatically higher in LPP." This may be a fundamental concept regarding parapsoriasis in medical dermatology practice. Much attention has been drawn to its malignant potential that may cause serious complications. Many investigations are focusing on the risk of malignant transformation in patients with parapsoriasis.

LPP is a well-known premycotic dermatosis. Prior studies demonstrated a progression to CTCL or MF in approximately 10–35% of LPP cases. The retiform parapsoriasis variant may have the highest risk among the LPP group. While most dermatologists consider LPP as a premycotic dermatosis, some authorities hypothesize that LPP is MF from the beginning. Controversy persists because LPP and MF overlap considerably both clinically and histopathologically [2, 6]. However, current evidence that strongly supports the hypothesis that "LPP is MF" is still not enough. Moreover, among patients who have a definitive diagnosis of MF, most do not have a history of preceding parapsoriasis.

The relationship between SPP and cutaneous lymphoma is more controversial. SPP was defined as a benign disease with no or minimal risk of malignant transformation. Some studies even documented that SPP never developed into MF or another lymphoma. Conversely, there are a few studies that have reported cases of SPP transforming into overt lymphoma. A retrospective study of 105 patients with parapsoriasis from Finland reported that 10% of patients with SPP developed MF over a median of 10 years. Additionally, there are case reports and a systematic review that support the malignant potential of SPP [6, 12, 13].

T-cell receptor gene [TCR] rearrangement analysis has been utilized to support the diagnosis of early-stage MF for at least 15 years. Monoclonality can be detected not only in malignancy but also in inflammatory skin diseases. However, it may be negative in MF or other cutaneous lymphomas as well. Hence, the results should be interpreted with caution. Detection of identical clones from two different skin sites is highly suggestive of MF.

The diagnostic dilemma remains controversial until the present day. Nevertheless, both conditions have an excellent prognosis and similar treatment plans. The survival rate and life expectancy are comparable to normal healthy populations. We propose a flowchart summarizing the approach to differentiate parapsoriasis and MF in Fig. 5.



(Figure No. 5)

Symptoms

Small plaque parapsoriasis usually presents as yellow-brown or pink, rash-like patches that are oval or round with scaling. The lesions mainly appear on the abdomen, legs, or extremities. SPP is otherwise asymptomatic. Plaques may also develop on areas of skin where specific nerves spread out from the spinal cord and appear on the abdomen and back. This is also known as digitate dermatosis, as the plaques resemble fingers or digits. Large plaque parapsoriasis usually causes larger, irregularly shaped patches that are brown or red with fine scaling. The skin in affected areas may also become thinner. People usually develop lesions in areas that have little exposure to the sun, such as the thighs, buttocks, breasts, and lower abdomen. LPP may be otherwise asymptomatic but may develop into skin cancer. The plaques in both types of parapsoriasis may have a wrinkled, thinning appearance.[12]

Diagnosis

For a doctor or dermatologist to diagnose parapsoriasis, a person's skin must show symptoms of either SPP or LPP. A doctor or dermatologist will usually perform a punch biopsy, a type of biopsy, on an affected area of the skin. This will allow them to see the full thickness of the skin and examine it under a microscope.

They may perform multiple biopsies in different areas of the skin, as parapsoriasis is a diverse condition. They may additionally recommend performing more biopsies over time to track and monitor how the condition progresses. Finding the right medical professionals to collect and make sense of your medical information can be challenging. Diagnosis may come through a primary care provider, or after specialized testing and referrals. Though the challenges are similar, everyone's diagnostic journey is different because everyone's story is too. [12, 13]

Treatment

A doctor or dermatologist will treat small plaque parapsoriasis with a moderate to high potency topical corticosteroid for 8–12 weeks.

If the rash does not clear by at least 50%, the doctor or dermatologist will consider the results unsatisfactory. They generally will then begin phototherapy treatment 2-3 times a week. With phototherapy, a healthcare professional exposes the person's skin to UVB light or UVA light. UVB light is a type of ultraviolet light on the spectrum between UVA rays, which cause tanning, and the more intense UVC rays. Phototherapy should not cause sunburn but may cause slight pinkness in the skin. A doctor or dermatologist may also treat SPP using emollients, which are skin moisturizers, and tar preparations such as coal tar products. Treatment for LPP is similar to SPP, starting with topical corticosteroids. However, a healthcare provider will usually prescribe a

very high-potency steroid for LPP, which the person should use for about 12 weeks.
If LPP is severe, a doctor will usually recommend phototherapy treatment 2–3 times a week. People should see a healthcare provider for follow-ups annually for SPP and every 6 months for LPP, due to the latter condition's potential to progress into cancer. [2]
Parapsoriasis is a chronic, indolent disease that may persist for many years. Most patients are asymptomatic and generally in good health. Most cases respond poorly to treatment. To date, there are no randomized controlled trials for the treatment of this condition. We summarize the current treatment for parapsoriasis.

Treatments for Parapsoriasis [14]
Table No. 1.

Medication	Mechanism of action
Topical therapy	
Corticosteroids	Anti-inflammation, inhibition of cell proliferation
Bexarotene	Inhibition of cell proliferation
Nitrogen mustard mechlorethamine or mustine	Inhibition of cell proliferation
Carmustine [BCNU]	Inhibition of cell proliferation
Hydrogen-water bathing	Anti-oxidation
Imiquimod	Immunomodulatory
Coal tar	Anti-inflammation, inhibition of cell proliferation, antibacterial, and antipruritic effects
Laser and light-based therapy	
BB or NB-UVB	Immunomodulatory, immunosuppression, apoptosis of T cells
UVA1	
PUVA	
Bath PUVA	
Topical PUVA	
Excimer laser [308 nm]	
Balneophototherapy	
Sunlight/ heliotherapy	

Discussion
Parapsoriasis is a chronic condition, meaning it can be recurring and lifelong. A person may need to seek a long-term management plan. While SPP is a benign condition, LPP may become malignant, and develop into the cancer mycosis fungoides, or cutaneous T-cell lymphoma [CTCL].
It can be difficult for a doctor to diagnose CTCL because:

- Blood tests may not reveal cancerous cells.
- It often looks like a common skin condition such as psoriasis or eczema
- A skin biopsy often does not reveal cancer cells.

Mycosis fungicides, the most common type of CTCL, develop slowly. This means that doctors or dermatologists diagnose about 70% of people while they are in the early stages of cancer. Someone who begins treatment in the early stages of cancer has a normal life expectancy.
If the cancer is more advanced, doctors will focus treatment on delaying the spread of cancer, reducing tumours, and improving the person's quality of life. Cancer may have no cure, but doctors can effectively manage it.
Conclusions
Parapsoriasis is the name for a collection of skin conditions that are similar to psoriasis. While the two appear similar and have similar treatments, parapsoriasis causes thinner scaly plaques than psoriasis. There are two types of parapsoriasis, which are known as large plaque and small plaque parapsoriasis. Large plaque parapsoriasis may become malignant, and develop into cancer called cutaneous T-cell lymphoma. Small plaque parapsoriasis is a benign condition that is unlikely to cause any other issues. Both types result in a pink or yellow-brown rash with scaly plaques on the skin.
A doctor or dermatologist will diagnose parapsoriasis by examining the skin, checking for symptoms, and most likely by performing a series of biopsies. They will

treat the condition with corticosteroids, followed by phototherapy if necessary. They also will carefully monitor the person for signs of skin cancer. Parapsoriasis is a chronic, lifelong condition that is possible to treat, but not cure. The large plaque variety may develop into an incurable but treatable cancer.

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Parapsoriasis—A Diagnosis with an Identity Crisis: A Narrative Review Manasmon Chairatchaneeboon,1 Kanchalit Thanomkitti,1 and Ellen J. Kim Dermatol Ther [Heidelb]. 2022 May; 12[5]: 1091–1102. Published online 2022 Apr 15. doi: 10.1007/s13555-022-00716-y

Pityriasis Rubra Pilaris

Curated by: Rushikesh Tagad
Guided by: Dr Revan Karodi HOD Department of Pharmacognosy

Abstract
It is an idiopathic papulosquamous inflammatory dermatosis known as Pityriasis rubra pilaris (PRP). It is distinguished by areas of sparing, palmoplantar keratoderma, and hyperkeratotic follicular papules aggregating into orange-red scaly plaques. According to Griffiths' categorization, PRP can be split into six clinical categories based on the age of onset, the severity of the disease, the prognosis, and other related characteristics. Retroviral testing is indicated in all de novo occurrences of PRP since the sixth subtype of PRP only affects people with HIV infection. Although the true relevance of these relationships is still unknown, other observed links include other diseases, autoimmune, medications, and cancers. The gain of function mutations in the caspase recruitment domain family, member 14 (CARD14) gene have been identified as the genetic basis for familial cases, which are most frequently grouped under the fifth category. The lack of high-quality evidence makes treating PRP a difficulty even today. Oral retinoids have been the backbone of treatment, with therapeutic regimens being primarily guided by case reports and case series. Biologics have just come to light as a viable PRP treatment. We discuss the clinicopathologic characteristics, aetiology, related disorders, and management of PRP with a focus on and critical evaluation of the material that has already been published on the subject.

Introduction
It is uncertain what causes Pityriasis rubra pilaris (PRP), an uncommon inflammatory papulosquamous illness. There are six different subtypes that appear in both children and adults with remarkable differences. Basic characteristics shared by all subtypes include distinct, well delineated plaques of different sizes and typical reddish-orange hues that may vary in magnitude. The "islands of sparing," which constitute a distinguishing feature of PRP, are frequently seen in more broad variants. A wide range of manifestations are possible, from mild disease limited to the extremities to severe disease that can occasionally progress to generalised erythroderma. [1-5]

Etiology
The precise cause of PRP is still unknown. Several instances of PRP-like eruptions have been linked to vaccinations or pharmaceutical use.

Epidemiology
PRP can happen to anyone, regardless of gender or ethnicity. The true incidence or prevalence of PRP is not well-documented in the literature. A British study put the frequency of new patient visits to a dermatologist in the outpatient setting at 1 in 5000, whereas an Indian study put it at 1 in 50,000. Dr. Andrew Griffith proposed a prevalence estimate of 2.5 million cases overall, or an average of 1 case per 400,000 people, in a speech to the British Society of Dermatology in 2003. With peaks in the first to second and fifth to sixth decades of life, there seems to be a bimodal age distribution. Although familial cases have been documented in up to 6.5% of cases, the majority of cases appear to be sporadic. In most instances, the pattern of familial inheritance appears to be autosomal dominant with varied penetrance. Yet, evidence of autosomal recessive patterns has also been found.

Sign and symptoms
Devergie disease
lichen ruber acuminatus
PRP
lichen acuminatus
pityriasis rubra pilaire (Fr.)
lichen ruber pilaris

Causes

Although the precise underlying cause of PRP is unknown, a genetic predisposition, an environmental trigger, and other unidentified reasons are thought to play important roles. It was formerly thought that the illness was caused by a vitamin A deficiency, however there is insufficient evidence to support this view, and vitamin A therapy has not been very successful.[6,7]

Pathophysiology

Although several well-known hypotheses exist, the pathogenesis of PRP is still unknown. These hypotheses include abnormal immunologic triggers like infection or ultraviolet (UV) exposure given evidence of phototriggered and/or photoactivated cases or trauma, dysfunction in keratinization or vitamin A metabolism, and autoimmune mechanisms. At least some cases of PRP appear to be influenced by genetics; this is most clearly seen in the type-V PRP variant. a definite correlation with a gain-of-function mutation in the CARD14 gene, also known as the psoriasis susceptibility gene (PSOR2), which produces the member 14 protein, an NF-kappa beta activator. In patients with sporadic PRP, comparable mutations have been discovered. Further investigation is required. Type-VI diabetes has been linked to the human immunodeficiency virus (HIV).[8,9]

Histopathology

PRP exhibits uneven, psoriasiform acanthosis of the epidermis on histological examination, accompanied with a distinctly recognisable "checkerboard" pattern of parakeratosis overlaying it (alternating vertical and horizontal ortho- and parakeratosis). There is frequently major follicular plugging along with shoulder parakeratosis. PRP can be distinguished from psoriasis by having thick suprapapillary plates as opposed to thin ones and by having no neutrophils in the stratum corneum. Although they have been described, focal acantholytic dyskeratosis, epidermal spongiosis, and variable mild superficial perivascular lymphohistiocytic infiltration are not always present.

Differential Diagnosis

Depending on the subtype, the differential diagnosis for PRP varies substantially. All papulosquamous conditions must generally be recognised from one another, particularly psoriasis.

While there are numerous combinations of certain indications and symptoms that can arise in PRP, each one needs to be taken into account and distinguished. The following list of typical findings and relevant differentials includes:

Scalp: PRP's early scalp illness can range from mild to severe, usually on an erythematous background. Its defining feature is the disease's rapid progression and severity. Should be recognised from the silvery, hyperkeratotic, waxy scale of psoriasis and the waxy scale of seborrheic dermatitis.

Palmoplantar keratoderma can be distinguished from psoriasis, ichthyosis, hereditary palmoplantar keratoderma, and erythrokeratodermia by its distinctive reddish-orange colour with varying accompanying edoema.

Nail changes: Psoriasis can frequently be misinterpreted for having yellow-brown hyperkeratotic nails with varying subungual debris. It is significant to note that PRP does not experience alterations to the proximal nail matrix or nail bed, such as nail pits or oil spots, which in many instances can help distinguish one from the other.

Erythroderma: While a biopsy is frequently required, a history alone may help distinguish PRP from other primary causes of generalised erythroderma. Psoriasis, atopic dermatitis, medication responses, cutaneous T-cell lymphoma, congenital ichthyosis, paraneoplastic diseases, and graft versus host disease are a few of the most well-known causes of erythroderma.

It is important to distinguish between atypical PRP, such as types II and V, and other types of acquired and congenital ichthyoses because they also exhibit ichthyosiform alterations.

When isolated, type-IV PRP spiny follicular papules can be mistaken for keratosis pilaris and lichen spinulosus. Eventually, the clinical trajectory ought to separate these entities.

Treatment / Management

In many cases, PRP is self-limited and asymptomatic therefore does not necessarily require treatment.

PRP treatment can be difficult, and there is no one method that works for everyone. The US Food and Drug Administration has not approved any treatments. The majority of medical professionals advise combining topical therapy for symptom management with systemic therapy intended to reduce inflammation. Emollients, keratolytic drugs such urea, salicylic acid, or alpha-hydroxy acid-containing preparations, topical corticosteroids, tazarotene, and topical calcineurin inhibitors are other topical treatments that have showed promise, particularly in mild illness. Oral retinoids are typically considered as the first-line systemic treatment for both adults and children. It has been demonstrated that oral isotretinoin at a dose of 1 to 1.5 mg/kg per day causes clearance in as short as 3 to 6 months. It has also been used regularly to administer methotrexate alone or in combination with oral retinoids. Nevertheless, systemic toxicity was more likely with combination therapy. Recent case reports and small case series have suggested a potential role for biologic immunosuppressive drugs, such as TNF-alpha inhibitors, secukinumab, and ustekinumab, which are generally used to treat psoriasis. Although there is a chance that a disease will be photo-triggered or -activated, narrowband UVB, UVA1, or PUVA light therapy has been used with some success in specific situations.

Conclusion

It's crucial to recognise and comprehend Pityriasis rubra pilaris as a disease. Psoriasis, seborrheic dermatitis, phrynoderma, atypical keratosis pilaris, follicular eczema, and erythrokeraderma are among the possible diagnoses (for example, Unna-Thost disease and Papillion-Lefevre syndrome).PRP has a variety of clinical manifestations, but there are treatments for each of them.It's critical to recognise the type of PRP a patient has and to administer the appropriate care.Thankfully, most patients who present with PRP have a good prognosis.

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Milk and Plant-Based Milk Alternatives: Know the Nutrient Difference

Curated by Sudhir Pandya
Assistant Professor Department of Pharmaceutics

The milk section of the dairy case isn't what it used to be. Along with milk, there's a growing variety of plant-based milk alternatives.

While many plant-based milk alternatives have the word "milk" in their name, the nutritional content can vary between the products, and many of them don't have the same amount of calcium and vitamin D or other nutrients as milk.

Soy beverages fortified with calcium, vitamin A and vitamin D are the only plant-based alternatives with a nutrient content similar enough to milk to be included in the dairy group. [1]

So, what should you look for when choosing plant-based milk alternatives?

The nutrients you get from plant-based milk alternatives can depend on which plant source is used, the processing methods, and added ingredients. Has the product been fortified with nutrients such as calcium? How much added sugar is in the product? What is the protein content?

The Nutrition Facts label on the packaging can help you compare the nutrient content of the various plant-based milk alternatives to milk. The label can help you choose the best products to meet your nutrient needs and those of your family.

Plant-Based Milk Alternatives

Although many plant-based milk alternatives are labelled with names that have the word "milk", these products are made from plant sources, not milk. The plant sources include: Grains such as oat, quinoa and rice, Legumes such as pea and soy, Nuts such as almond, cashew, coconut, hazelnut, macadamia, peanut, pistachio and walnut, Seeds such as flax, hemp and sesame, Because these are non-dairy products, they may offer an option for people who are allergic to milk or want to avoid dairy products for dietary reasons or personal preference. If one is choosing a plant-based milk alternative because of calories, he/she should check the nutrition label because some alternatives may actually be higher in calories than non-fat and low-fat milk, or may be much lower in protein than milk. [2]

Key Nutrients

Dairy foods, including milk and fortified soy beverages, are recommended in the Dietary Guidelines as part of a healthy dietary pattern. Dairy foods provide important nutrients that include protein, calcium, vitamin A, vitamin D, magnesium, phosphorus, potassium, riboflavin, vitamin B12, zinc, choline, and selenium. Three of these nutrients — calcium, potassium and vitamin D — are among those flagged by the Dietary Guidelines as dietary components of public health concern because people aren't consuming enough of them. Soy

beverages fortified with calcium, vitamin A, and vitamin D are included in the dairy group in the Dietary Guidelines because they are similar to milk based on their nutrient composition and use in meals. Other plant-based milk alternatives may have calcium and be a source of calcium, but they aren't included in the dairy group because their overall nutritional content isn't similar to milk or fortified soy milk, according to the Dietary Guidelines.

Using the Nutrition Facts Label [3]

Some of the key nutrients found in dairy products are required to be listed on the Nutrition Facts label, including calcium, vitamin D and potassium. Here are the nutrients you can find on the label and why they are important to your health:

- Choose milk and plant-based milk alternatives that are higher in protein, vitamin D, calcium and potassium.
- Protein builds bones, muscles, cartilage, skin, blood, enzymes, hormones and vitamins.
- Vitamin D maintains proper levels of calcium and phosphorus, which can help build and maintain bones.
- Calcium builds bones and teeth in children and maintains bone strength as you age.
- Potassium may help maintain blood pressure and is needed for proper muscle, kidney and heart function.
- Choose milk and plant-based milk alternatives that are lower in saturated fats and added sugars.
- Saturated fats may increase the risk of heart disease.
- Added sugars may make it hard to meet nutrient needs and stay within calorie limits.

There are special considerations for infants and young children to make sure they get the nutrients they need:

- Infants should not consume milk or plant-based milk alternatives before age 12 months to replace human milk or infant formula.
- Children ages 12 months through 23 months can be offered whole milk or fortified, unsweetened soy milk to help meet calcium, potassium, vitamin D and protein needs.

Reference

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[2] The New Nutrition Facts Label, FDA
[3] Draft Guidance for Industry: Labelling of Plant-based Milk Alternatives and Voluntary Nutrient Statements, FDA

Alpha-mannosidosis

Curated by Sudhir Pandya
Assistant Professor Department of Pharmaceutics

Alpha-mannosidosis is a rare inherited disorder that causes problems in many organs and tissues of the body. Affected individuals may have intellectual disability, distinctive facial features, and skeletal abnormalities. Characteristic facial features can include a large head, prominent forehead, low hairline, rounded eyebrows, large ears, flattened bridge of the nose, protruding jaw, widely spaced teeth, overgrown gums, and large tongue. The skeletal abnormalities that can occur in this disorder include reduced bone density (osteopenia), thickening of the bones at the top of the skull (calvaria), deformations of the bones in the spine (vertebrae), knock knees, and deterioration of the bones and joints.

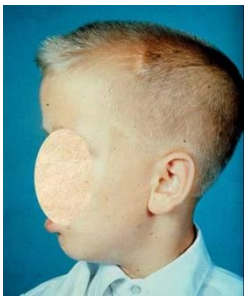
Affected individuals may also experience difficulty in coordinating movements (ataxia); muscle weakness (myopathy); delay in developing motor skills such as sitting and walking; speech impairments; increased risk of infections; enlargement of the liver and spleen (hepatosplenomegaly); a buildup of fluid in the brain (hydrocephalus); hearing loss; and a clouding of the lens of the eye (cataract). Some people with alpha-mannosidosis experience psychiatric symptoms such as depression, anxiety, or hallucinations; episodes of psychiatric disturbance may be triggered by stressors such as having undergone surgery, emotional upset, or changes in routine.

The signs and symptoms of alpha-mannosidosis can range from mild to severe. The disorder may appear in infancy with rapid progression and severe neurological deterioration. Individuals with this early-onset form of alpha-mannosidosis often do not survive past childhood. In the most severe cases, an affected fetus may die before birth. Other individuals with alpha-mannosidosis experience milder signs and symptoms that appear later and progress more slowly. People with later-onset alpha-mannosidosis may survive into their fifties. The mildest cases may be detected only through laboratory testing and result in few if any symptoms.

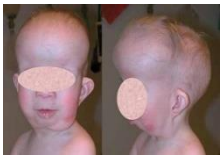
Mutations in the MAN2B1 gene cause alpha-mannosidosis. This gene provides instructions for making the enzyme alpha-mannosidase. This enzyme works in the lysosomes, which are compartments that digest and recycle materials in the cell. Within lysosomes, the enzyme helps break down complexes of sugar molecules (oligosaccharides) attached to certain proteins (glycoproteins). In particular, alpha-mannosidase helps break down oligosaccharides containing a sugar molecule called mannose.

Mutations in the MAN2B1 gene interfere with the ability of the alpha-mannosidase enzyme to perform its role in breaking down mannose-containing oligosaccharides. These oligosaccharides accumulate in the lysosomes and cause cells to malfunction and eventually die. Tissues and organs are damaged by the abnormal accumulation of oligosaccharides and the resulting cell death, leading to the characteristic features of alpha-mannosidosis.

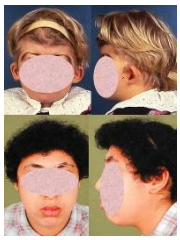
Note the increased size of the cranium.



Differences in size are difficult to appreciate but increased head size in this child is notable because of comparison with the smaller face.

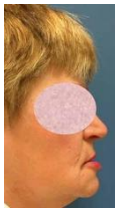


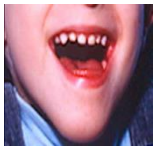
The entire forehead is prominent due to protrusion of the frontal bone.



The low anterior hairline contributes to an appearance of short forehead.

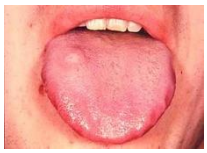
There is anterior protrusion of the mandible such that the alveolar ridge extends beyond the vertical plane of the maxillary alveolar ridge.

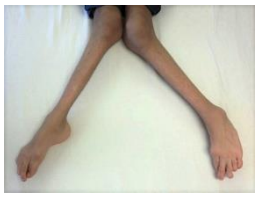




Widely spaced teeth

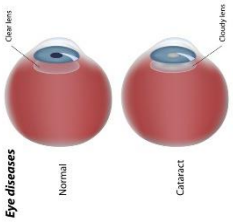
Large tongue (macroglossia)

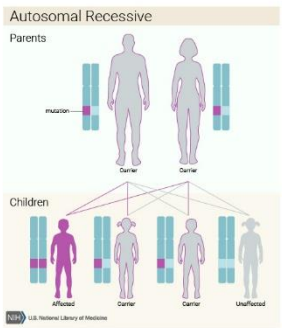




Knock knees (genu valgum)

Cataract





This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations.

The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

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REVIEW ARTICLE ON KLINEFELTER SYNDROME

Curated by- Bapat Sai Shrikant, Jadhav Varsha Rajendra
Under guidance of – Dr. Mrs. Sonali P. Mahaparale.
Quality Assurance Techniques,

The first ever Klinefelters syndrome (KS) awareness day was celebrated on 10th May 2022. [1] Sometimes KS is associated with language problems and learning disabilities. It is also called as 47 XXY.

Keywords: Klinefelter syndrome, male infertility, chromosome abnormality.

INTRODUCTION:

Klinefelter syndrome is named after the Dr. Henry Klinefelter, who identified this condition in the early 1940s. Normally, every cell in a male's body, except sperm and red blood cells, contains 46 chromosomes, but males containing this syndrome have 47 chromosomes. Usually male contains XY chromosomes but in KS syndrome have an extra X chromosome, which makes them 47 XXY (karyotype). [2][6]

Klinefelter syndrome is a congenital condition, which means it's present

from the time of birth. But many men (some say 70 to 80%) likely don't know they have this condition.

ETIOLOGY:

KS occurs when a male baby is born

with at one extra X chromosome. This imbalance is due to an error during egg or sperm development and causes in a male having an extra X chromosome in all of his body's cells. It is a genetic disorder. KS is found in about 1 in 500 to 1,000 newborn males.

SIGNS AND SYMPTOMS:

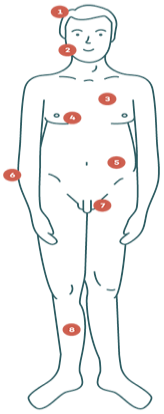
In babies, symptoms are hernia, slower to learn to sit, crawling, and talk. Testies does not drop into scrotum. [5]

Boys in their teenage have behavior changes like mostly stay quite, sensitive, unassertive. [6] Get taller than other normal boys (1) and have more belly fat than their peers (5). They are slow in learning, talking, reading, and have difficulties in hearing. [7]

They have small penis size (7), less muscle tone, wider hips, varicose veins (8), etc.

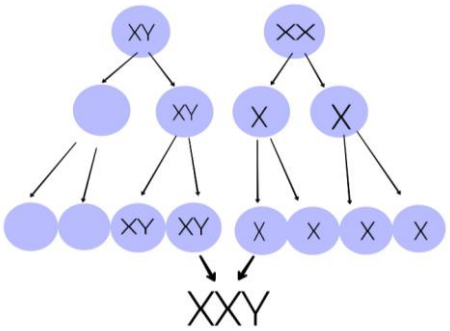
Male having KS shows signs low testosterone levels, low sex drive, infertility, breast development (4) (gynecomastia), reduced muscle mass (6), broad hips, weaker bones, reduced body hair (3) and facial hairs(2), etc.

Following figure shows symptoms of KS with numbers listed 1-8 above.



PATHOPHYSIOLOGY:

As shown in following figure, the XY nondisjunction in male fertilizes with normal womens X chromosome in meiosis II phase to produse trisomy XXY (47).



COMPLICATIONS:

There are some complications such as heart disease, diabetes, osteoporosis, autoimmune disorders (including lupus),

cancer (including breast cancer), lung disease, varicose veins, dental cavities, anxiety and depression. [8]

DIAGNOSIS:

Genetic test can diagnose KS. 1. Karyotype Test - A small skin or blood sample is sent to a laboratory to find out if there is an extra X chromosome. [5]

2.In puberty a physical examination of the chest and testes such as small testes and enlarged breasts shows presence of KS.

3. Sperm count test- It is done for reduced fertility and a hormone test for reduced testosterone.

Only 10 % Trusted Source of cases are diagnosed in childhood, while on average, males with KS are not diagnosed until their mid-30s. Sometimes because of similar symptoms of other diseases, KS remains undiagnosed.

TREATMENT:

KS can't be cure but can reduces symptoms by treatments.

1. Testosterone replacement therapy- It is done by using an injection, pills, gel, or a patch. It improves strength, body hair growth, energy, and concentration. Testosterone therapy does not improve testicle size or fertility. [3][5]

2. Fertility treatment - 95 - 99 % of males with KS are infertile because they can't produce enough sperm to fertilize an egg. For those males, an intracytoplasmic sperm injection (ICSI) is effective. During an ICSI, sperm is removed from the testicle and injected directly into the egg. [4][8]

3. Cryopreservation - If KS is diagnosed earlier, semen or testicular tissue can be preserved before the testicular damage starts, probably at puberty.

4. Breast reduction surgery- There is no approved drug treatment for overdeveloped breast tissue in males. Removal of the breast tissue by a plastic surgeon is effective but comes with the risks. But it reduces the chances of developing breast cancer. [8]

5. Psychological counseling and speech therapy, physical therapy, educational evaluation, behavioral therapy. [4][6]

CONCLUSION:

The Klinefelter's syndrome is frequent and, if not diagnosed (which seems to be the most common case), these men have higher risks to develop psychiatric disorders. The diagnosis of KS would be less frequently missed if doctors were more aware of, and attentive to, its key manifestations, particularly the small, firm testes, erectile dysfunction, and the comorbidities mentioned above. So the conclusion is that if the diagnosis were made more often, patients would more often be able to receive early treatment, which would improve their quality of life. Klinefelter syndrome 47 XXY was first described 70 years ago (1). With an incidence of 0.1% to 0.2% of male neonates (i.e. 1 to 2 per 1000), it is one of the commonest congenital chromosome disorders resulting in hypogonadism and genetically-determined infertility.

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Sarcoidosis

Curated by – Miss Poonam R. Mulay
Department of Pharmaceutical Chemistry

Every year on April 30th, World Sarcoidosis Day is observed to increase global sarcoidosis consciousness and improve sarcoidosis care.

Introduction:

Sarcoidosis, is a condition where abnormal inflammatory cell clusters develop that forms lumps called granulomata. At the King's College Hospital in London, John Hutchinson reported the first case of sarcoidosis in 1877. (United Kingdom).Sarcoidosis also called Besnier-Boeck-Schaumann disease, because Besnier et al. published the first description of sarcoidosis in 1889. [1] The disease usually starts in the lungs, skin, or lymph nodes. [2] Less commonly affected are the eyes, liver, heart, and brain, though any organ can be affected. [3] The mechanisms driving granuloma formation, including genetic susceptibility and environmental influences, are becoming more and more understood, even though sarcoidosis is still a disease with an unknown origin. [4]

The medical and scientific communities, as well as the general population, are generally uninformed about sarcoidosis, and as a result, many patients receive incorrect diagnoses. It is critical to deal with sarcoidosis as soon as possible because it can significantly lower a person's quality of life. Regrettably, sarcoidosis receives less funding from the federal government for study than other inflammatory diseases, even ones that are less common. Alternative funding sources are required to help those who work in the sarcoidosis field enhance the care and quality of life for those who have the disease. The survival rate of sarcoidosis patients is lower than that of the general population.

Epidemiology:

The prevalence and incidence of sarcoidosis are not well recognised on a global scale due to the difficulties in determining the number of asymptomatic patients. Sarcoidosis impacts all ages irrespective of race or ethnicity. It is most common in those aged 20 to 39 and is far more common in women, non-smokers, and rural areas. African Americans suffer from the greatest incidence (17-35 reported yearly incidence per 100,000 population), followed by Whites (5-12 reported annual incidence per 100,000 population), while Asians and Hispanics experience the lowest reported annual incidence (1-3 per 100,000 population). [5, 6] In as many as 25 to 30 percent of patients, extrapulmonary sarcoid is detected. Males are more likely to experience cardiac involvement, while females have more noticeable skin and ocular traits. Extrapulmonary characteristics can vary depending on the age of presentation, the gender, and the ethnicity. [7, 8]

Etiology

It is an inflammatory condition with an unidentified etiology that shows up as non caseating granulomas in several systems. There have been many links reported, including work-related and ambient exposures to beryllium, dust, and other asthma-causing chemicals. Many microbes, including propionibacteria and mycobacteria, have been linked. A few investigations where sarcoidosis occurred in a previously negative person after heart or bone marrow transplantation have indicated a potential infectious cause. [9]

Antigens of the major histocompatibility complex (MHC), particularly DR alleles, are typically associated to genetic components and disease in more than one family member. Sarcoidosis is intimately related to cytokines like Th1, IL-2, IL-6, IL-8, IL-12, IL-18, IL-27, interferon (IFN) gamma, and tumour necrosis factor (TNF) alpha.

Signs and Symptoms of Sarcoidosis :

The symptoms and signs differ according to the organ involved. [2] In many cases, there are no or very little symptoms.

General Symptoms of Sarcoidosis:

- Fatigue: Sarcoidosis is not the only cause of fatigue; other conditions like hypothyroidism, anxiety, depression, sleep apnea, or an active and severe inflammatory response can also contribute to fatigue.
- Fever and Unexplained weight loss
- Night sweats
- Joint pain

- Kidney stone

Symptoms of Sarcoidosis of Heart:

- Chest pain
- Heart failure
- Shortness of breath
- Irregular Heartbeat

Symptoms of Sarcoidosis of Lungs:

- Wheezing
- Cough
- Chest Pain
- Dypsnea

Symptoms of Sarcoidosis of Skin:

- Raised, reddish-purple sores or rash across your nose or cheeks.
- Red, tender bumps on your shins
- Light or dark patches of skin.
- Growths under your skin around scars or tattoos.

Symptoms of Sarcoidosis of Nervous System:

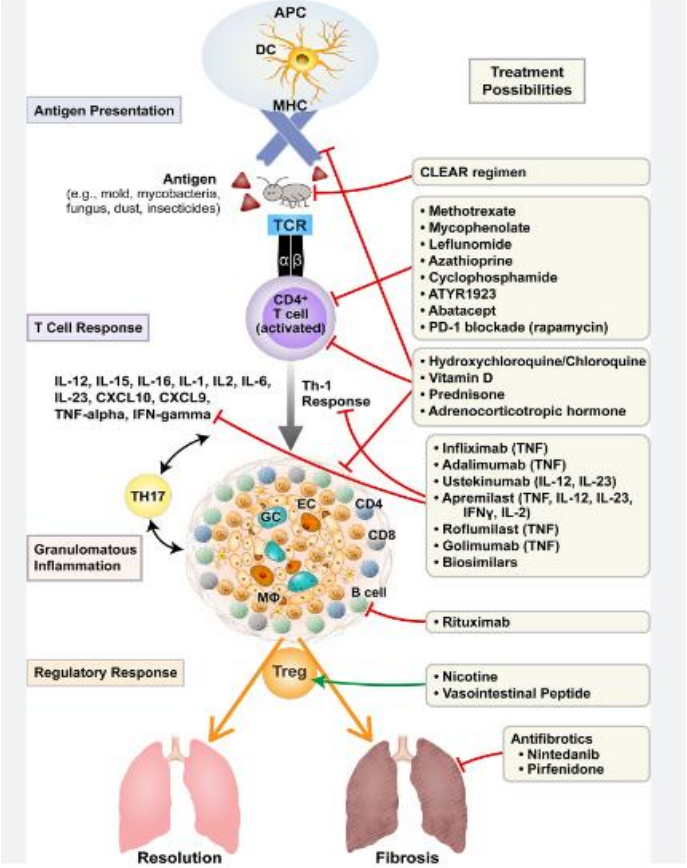
- Seizures
- Headaches
- Diabetes insipidus
- Weak or paralyzed facial muscles

Symptoms of Sarcoidosis of Eyes:

- Eye pain
- Sensitivity to light
- Red or swollen eye
- Loss of vision or Blurred vision

Pathophysiology of Sarcoidosis:

Narrow sarcoidosis has a complex pathogenesis that is influenced by both genetic and environmental factors. T cells, which increase cellular immunological response and frequently have an inverted CD4/CD8 ratio, play a crucial role in the onset of sarcoidosis. It is distinguished by a noncaseating granuloma that typically contains lymphocytes, monocytes, mast cells, and fibroblasts along with macrophages, multinucleated giant cells, and epithelioid cells. Tumor necrosis factor (TNF) and TNF receptors play a part in this condition since both are elevated. The function of anti-TNF medications like pentoxifylline and infliximab has served as proof of this. B cell hyper reactivity with immunoglobulin synthesis is also implicated, in addition to the function of T cells. Plasmatic hypergamma globulinemia has also been linked to active sarcoidosis. Elevated serum concentrations of soluble HLA class I antigens and angiotensin-converting enzyme (ACE) levels were associated.



Diagnosis:

A physical examination, imaging (such as a chest X-ray), and biopsy of suspicious granulomas are typically used to diagnose sarcoidosis. physician might recommend additional testing to rule out other illnesses because sarcoidosis can resemble other disorders.

Test Used to diagnosis Sarcoidosis:

The most common methods for diagnosing sarcoidosis include imaging tests and biopsies

Imaging tests: It is use specialised equipment to take photographs of the internal body structures. A medical professional may request a chest X-ray, CT scan, or MRI.

Biopsies: Depending on whether there are granulomas, biopsies can be performed in a variety of ways. It is possible for skin, conjunctiva (eye), and some lymph node biopsies to be minimally or non-invasive.

Small tubes, cameras, and biopsy equipment can be used during more extensive operations to evaluate lung tissue when they are passed

through the nose, throat, or an incision (small cut). They consist of:

- Bronchoscopic transbronchial biopsy
- Endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA)
- Mediastinoscopy

Other test for Sarcoidosis may include:

- **Lab tests:** liver, kidneys, and other organs' functionality is evaluated using blood or urine tests.
- **Nuclear imaging:** PET scans and gallium scans indicate inflammation in body by injecting a small amount of radioactive material into a vein.
- **Electrocardiogram (EKG or ECG):** A common test that checks the electrical activity of heart.
- **Purified protein derivative:** A quick skin test to determine previous tuberculosis exposure or infection (TB). This can identify or rule out TB, which is occasionally confused with sarcoidosis.

Treatment:

The goal of sarcoidosis treatment is typically to control symptoms and stop organ damage. Because immune cells generate inflammation in granulomas, sarcoidosis is typically treated with drugs that alter or suppress the immune system. Therapy is based on the location of granulomas in body.

Sarcoidosis has no known treatment however it frequently goes away on its own. Sarcoidosis occasionally doesn't need to be treated right away if symptoms aren't uncomfortable or life-threatening.

Pharmacotherapy:

Medicines used to treat Sarcoidosis: Sarcoidosis medications work to lower inflammation by altering or suppressing y immune system. Among the drugs frequently prescribed for sarcoidosis are:

Anti-tumor necrosis factor-alpha antibodies (anti-TNF-alpha antibodies): Similar to infliximab, anti-TNF-alpha antibodies work to reduce inflammation by focusing on a particular immune system molecule. A medical professional administers these medications by injecting them directly into your vein.

NSAIDs: Non-steroidal anti-inflammatory drugs NSAIDS are drugs that can provide momentary symptom alleviation from inflammation. They are typically not recommended for prolonged use.

Corticosteroids: Prednisone and cortisone are examples of corticosteroids, which are medications that lessen inflammation in the body. They come in the form of oral pills, inhalers you use to breathe through your mouth, or topical lotions (applied directly to your skin or eyes).

Immunosuppressants: Immunosuppressants assist in preventing organ damage and inflammation brought on by the immune system. One immunosuppressant frequently prescribed for sarcoidosis is methotrexate.

Sarcoidosis can cause many complications, including:

- Osteoporosis.
- Depression and emotional irritability.
- Skin bruising.
- Diabetes in susceptible people.
- High blood pressure.
- Glaucoma.
- Cataracts.
- Excessive weight gain.
- Insomnia.
- Acne.

Conclusion:

Many patients with Sarcoidosis do not require treatment, and the condition resolves on its own. However, in a small number of people, the diseases can progress to a fulminant stage with severe symptoms. Significant chest imaging findings, extrapulmonary involvement, and the presence of pulmonary hypertension are all indicators of a poor prognosis. Sarcoidosis, whether symptomatic or not, acute or chronic, can affect a variety of organs and have a range of clinical consequences ranging from mild to severe. Future research must elucidate the genetic and environmental determinants of such

phenotypes in order to better understand the pathophysiology of sarcoidosis and, eventually, to guide treatment.

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Systemic Capillary Leak Syndrome

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Introduction

Systemic capillary leak syndrome (SCLS), also called **Clarkson's disease**, or primary capillary leak syndrome, is a rare, grave. It is medical condition observed largely in otherwise healthy individuals mostly in middle age. The term capillary leak syndrome has been used to describe this constellation of disease manifestations associated with an increased capillary permeability to proteins. [1].

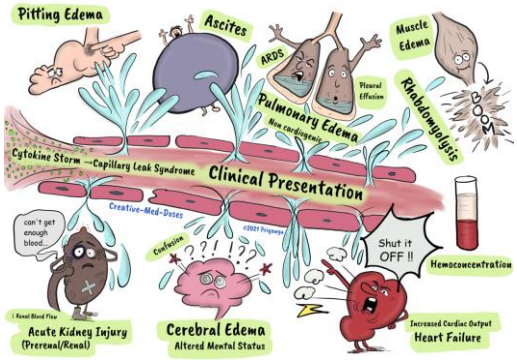

Fig. Diagrammatic presentation of systemic capillary leak syndrome [2]

Acute SCLS episodes carry a high morbidity and mortality (25-30%). Fewer than 500 cases have been reported worldwide since 1960, although the disease may be underdiagnosed due to the nonspecific nature of the presenting signs and symptoms and the considerable overlap with other shock syndromes including sepsis, anaphylaxis, and angioedema. Approximately 85% of such individuals have a monoclonal gammopathy of unknown significance (MGUS), but the relationship of this finding to disease pathogenesis is unclear. This protocol will focus on the pathogenesis of SCLS. Subjects with documented episodes of capillary leak will be evaluated in order to correlate both clinical and laboratory features that are typical of SCLS. The goal is to identify biological factors and/or genetic and molecular events that may predispose to SCLS episodes [3].

Cause

Its cause is unknown, although it is believed to be a manifestation of transient endothelial dysfunction due to endothelial contraction, apoptosis, injury, or a combination of these [4].

Symptoms

The most common prodromal symptoms described are as follows

Flu-like symptoms

1. Abdominal pain
2. Dizziness
3. Nausea
4. Vomiting

Further symptoms observed in patients are polydipsia, dizziness, hypotension, generalized edema (as well as cerebral, pulmonary, macular or epiglottic edema), weight gain, pleural or pericardial effusion, and renal dysfunction that could end in renal failure [4].

Pathogenesis

All of the diseases causing capillary leak syndrome share the same underlying pathophysiologic abnormality an increase in capillary permeability to proteins, 8, 9, 18, 30, 64. As a result, there is a loss of protein-rich fluid from the intravascular to the interstitial space. In all cases, hypercytokinemia is believed to be the underlying cause of capillary leak. In a study of a patient with SCLS, Atkinson et al. estimated that substances in the plasma of at least 200 kDa, but not more than 900 kDa, were leaked into the interstitial space. (For comparison, albumin has a molecular weight of 66.5 kDa.) In their study, Atkinson *et al.*9 measured a 30% to 50% loss of albumin from the intravascular space during the first 12 hours of the capillary leak phase. [3], [8].

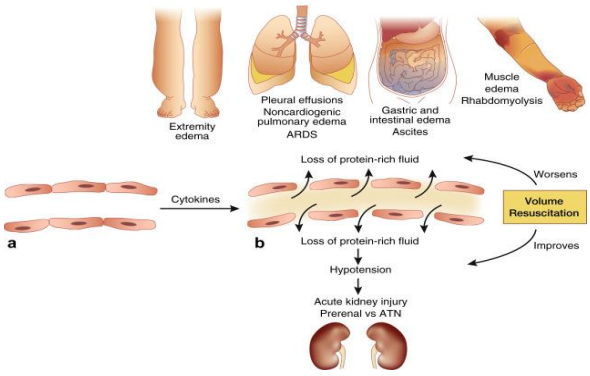

Figure 2. Clinical manifestations of capillary leak syndrome [8]

Complications

Complications may include compartment syndromes, renal failure from hypoperfusion-induced acute tubular necrosis or myoglobinuria secondary to rhabdomyolysis and venous and arterial thrombosis, including pulmonary embolism and also complications can include general swelling, compartment syndrome, kidney failure, and stroke. SCLS occurs in episodes which vary in frequency, with some people having one episode in their lifetime and others having several per year. The severity also varies, and the condition can be fatal. [5]

Treatment

Treatment for systemic capillary leak syndrome (SCLS) is focused on managing the symptoms during an episode and preventing long term complications. During an episode, treatment involves stabilizing the airway and breathing using medications, hydration, and oxygen therapy. Physiotherapists will be involved in oxygen administration and management of respiratory complications. See Physiotherapist role in ICU

Acute episodes are treated with vasopressor therapy and judicious fluid replacement, possibly with colloid solutions for their osmotic effects, to prevent the sequelae of under perfusion. Between episodes, patients may be treated with theophylline and terbutaline, which clinical experience suggests may reduce the severity and frequency of acute episodes.

Patients who have been diagnosed with SCLS tend to be carefully given fluids to manage their symptoms, and some patients have improved after being given intravenous immunoglobulin (the protein from which antibodies are made). This seems to prevent further episodes, highlighting the immune system's likely role in the disease [6].

Prevention

You can't prevent systemic capillary leak syndrome from developing. Once you've had an attack, you know you have the condition.

Regular use of medications or infusions may help prevent future episodes and reduce their severity.

In patients with SCLS, i.v. Ig is currently the most promising therapy for both acute treatment and long-term prevention. Doses of 2 g/kg monthly of i.v. Ig are the most commonly used for prevention [7].

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Wilson's disease

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Wilson's disease (WD) is a rare hereditary disease caused by mutations in the *ATP7B* gene, which encodes a transmembrane copper-transporting ATPase that inhibits the body from eliminating extra copper, causing copper to accumulation in the liver, brain, eyes, and other vital organs [1]. Copper plays a significant role in the growth of healthy nerves, bones, collagen and the skin pigment melanin. Usually, from food copper is absorbed and excess is removed through a bile that is produced in liver. But in individuals with WD, copper isn't eliminated appropriately and instead accumulates, probably to a life-threatening level. WD is erratic, with the incidence of symptomatic disease projected to be 1 in ~30,000 with a carrier frequency of 1 in every 90; however, a greater incidence of genetic WD has been observed according to current molecular studies. Some peoples have a higher occurrence of WD due to the increased rate of consanguineous marriages. The males and females both are affected equally.

Homozygous, or, more frequently, compound heterozygous mutations lead to faulty incorporation of copper into apo-ceruloplasmin and the following formation of holoceruloplasmin, hindering the regular excretion of copper into bile. Consequences of this defect are the reduced copper metabolism and following copper intoxication. With a shorter half-life than that of holoceruloplasmin, circulating apoceruloplasmin are abnormally low, albeit the gene accountable for this protein, restricted on chromosome 3, is intact, providing one of the most significant clinical diagnostic tools for WD. When diagnosed primary stage, WD is curable, and many individuals with the disease live normal lives. Most individuals with WD are diagnosed between the ages of 4 and 40, as well as it can affect younger and adult individuals old as 70.

Symptoms:

WD is existing from the birth, but signs and symptoms do not observe until the copper level builds up in the brain, liver or other vital organs. [2]. Signs and symptoms differ depending on the parts of body affected by the disease. They can include:

- Lack of appetite, Fatigue, or abdominal pain
- A yellowing of the skin and the whites of the eye like jaundice
- Golden-brown eye discoloration is known as Kayser-Fleischer rings
- In the legs or abdomen Fluid accumulation
- Problems related with speech, swallowing or physical coordination
- Uncontrolled movements or muscle stiffness

Causes:

WD is genetic as an autosomal recessive trait, which means that to progress the disease you must inherit one copy of the defective gene from each parent. If receive only one abnormal gene, that individual would not become ill but he/she is carrier and can pass the gene to their children. Increase the risk of WD if parents or siblings have such condition. Ask the doctor whether there is need of genetic testing to find out if individual have WD. Diagnosing the condition in early stage melodramatically rises the chances of effective treatment.

Complications:

Untreated, WD can be deadly. Serious complications include:

- **liver cirrhosis:** When liver cells attempt to make repairs to damage caused due to excess copper, scar tissue forms in the liver, making it more problematic for the liver to function normally.
- **Liver failure:** This can occur unexpectedly in acute liver failure, or it can develop slowly over years. A liver transplant might be an option as a treatment.
- **Persistent neurological problems** Tremors, involuntary muscle movements, clumsy gait and speech difficulties usually improve with treatment for WD. However, some individuals have persistent neurological difficulty despite treatment.
- **Kidney problems:** WD can damage the kidneys, leading to problems such as

kidney stones as well as an abnormal number of amino acids excreted in the urine.

- **Psychological complications:** These might comprise personality changes, bipolar disorder or psychosis, depression, irritability.
- **Blood problems:** These might include destruction of red blood cells leading to anemia and jaundice.

Treatment:

Doctors treat WD with chelating agents and zinc. People who have WD need lifelong treatment to manage symptoms and decrease or prevent organ damage. If WD causes acute liver failure or cirrhosis with liver failure, it may need a liver transplant.

Nutrition: If person have WD, talk with doctor about the diet and foods that contain copper. When start the treatment for WD, doctor may recommend avoiding foods that are high in copper content, such as chocolate, liver, mushrooms, nuts, and shellfish.

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WOUND HEALING: An Overview

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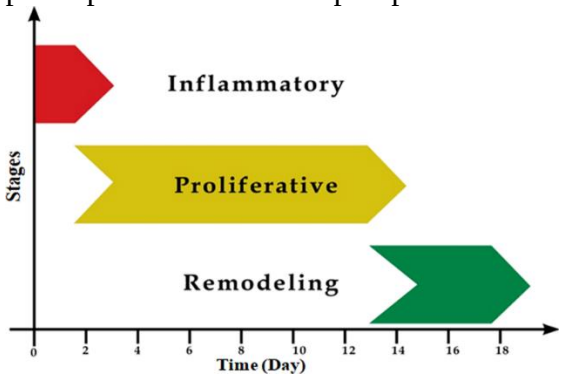
Background:-
Regeneration and tissue repair processes consist of a sequence of molecular and cellular events which occur after the onset of a tissue lesion in order to restore the damaged tissue. The exudate, proliferative, and extracellular matrix remodelling phases are sequential events that occur through the integration of dynamic processes involving soluble mediators, blood cells, and parenchymal cells. Exudative phenomena that take place after injury contribute to the development of tissue oedema. The proliferative stage seeks to reduce the area of tissue injury by contracting myofibroblasts and fibroplasia. At this stage, angiogenesis and reepithelialisation processes can still be observed. The purpose of this review is to describe the various cellular and molecular aspects involved in the skin healing process.

Keywords: Cell proliferation; Inflammation; Wound Healing.

Introduction:
Cutaneous wound healing is an essential physiological process consisting of the collaboration of many cell strains and their products. [1] Attempts to restore the lesion induced by a local aggression begin very early on in the inflammatory stage. In the end, they result in repair, which consists of the substitution of specialized structures brought about by the deposition of collagen, and regeneration, which corresponds to the process of cell proliferation and posterior differentiation through pre-existing cells in the tissue and/or stem cells.[2] These mechanisms do not mutually exclude themselves, that is, after a skin lesion, in the same tissue, regeneration and repair can occur, depending on the cell strains compromised by the injury. Tissue regeneration and repair processes occur after the onset of the lesion. Be that due to the trauma or resulting from a specific pathological condition. One lesion is created by all of the stimuli that break the physical continuity of functional tissues. The stimuli that cause lesions can be external or internal, as well as physical, chemical, electric, or thermal. Moreover, the lesions can result in damage to specific organelles or to cells as a whole. [3] Tissue repair is a simple linear process in which the growth factors cause cell proliferation, thus leading to an integration of dynamic changes that involve soluble mediators, blood cells, the production of the extracellular matrix, and the proliferation of parenchymal cells. The skin healing process, according to Mitchel et al., illustrates the principles of repair for the majority of tissues.[3] Cell and biochemical events in wound repair can be divided into the following stages: inflammatory reaction, cell proliferation and synthesis of the elements which make up the extracellular matrix, and the posterior period, called remodelling. [4] These stages are not mutually excluding, but rather overlap over time (Graph 1). [3] This literature review aims to highlight the biological processes involved during wound healing, with emphasis on the cells, growth factors, and cytokines that participate in the tissue repair process.



Graph 1: Sequential illustration of the stages involved in tissue repair

INFLAMMATORY STAGE
In a vascular inflammatory response, the lesioned blood vessels contract and the

leaked blood coagulates, contributing to the maintenance of its integrity. The coagulation consists of an aggregation of thrombocytes and platelets in a fibrin network, relying on the action of specific factors through the activation and aggregation of these cells. [5] The fibrin network, in addition to re-establishing homeostasis and forming a barrier against the invasion of microorganisms, organizes the necessary temporary matrix for cell migration (Figure 1), which in turn restores the fibroblast proliferation. Cell response in the inflammatory stage is characterized by the influx of leukocytes in the wound area (Figure 2). Such a response is very quick and coincides with the key signs of inflammation, which are revealed by the oedema and the erythema at the location of the lesion. Normally, cell response is established within the first 24 hours and can extend for up to two days. A quick activation of the immune cells in the tissue may also occur, as happens with mastocytes, gamma-delta cells, and Langerhans cells, which secrete chemokines and cytokines. Inflammation is a localized and protective tissue response that is unleashed by the lesion, causing tissue destruction. Inflammatory cells play an important role in wound healing and contribute to the release of lysosomal enzymes and reactive oxygen species, as well as facilitate the clean-up of various cell debris. [6] Buckley argues that the interaction of leukocytes and stromal cells during an acute inflammatory response resolves around the inflammatory focus. [7] Neutrophils are known for expressing many pro-inflammatory cytokines and a large quantity of highly active antimicrobial substances, such as reactive oxygen species (ROS), cationic peptides, and proteases at the location of the lesion. The inflammatory response continues with the active recruitment of the neutrophils in response to the activation of the complement system, function as a protective barrier, maintaining the skin's integrity. This also makes it possible for cell migration to the lesion's microenvironment and the stimulation of platelet degranulation, and bacterial degradation products. [8] These are attracted by many inflammatory cytokines produced by activated platelets, endothelial cells, and degradation products of pathogenic agents. [9] In this manner, the neutrophils are the primary activated and recruited cells that play a role in the clean-up of the tissue, as well as contribute to the death of invading agents. [3] Only a few hours after the lesion, a quantity of neutrophils transmigrate through the endothelial cells present in the blood capillary walls, which are activated by pro-inflammatory cytokines, such as IL-1 β, TNF-α (tumour necrosis factor alpha), and IFN-γ (interferon gamma) at the location of the lesion. Such cytokines promote the expression of many classes of adhesion molecules. These adhesion molecules are a determining factor for the diapedesis of neutrophils, including selectins and integrins - (CD11a/CD18 (LFA-1); CD11b/ CD18 (MAC-1); CD11c/CD18 (gp150, 95); CD11d/CD18) - which interact with those already present on the membrane surface of endothelial cells. The referent cells also influence many other aspects of tissue repair, such as the resolution of fibrin and extracellular matrix coagulation, the prompting of angiogenesis, and reepithelialization. As of 48 hours after the onset of the lesion, the migration of monocytes from neighbouring blood vessels, which also infiltrate the lesion area, is intensified, and, with the generation of the new genic expression profiles, are differentiated into macrophages. These, which are activated through chemokine signaling, can act as cells that present antigens and that aid neutrophils in phagocytosis. Thus, in addition to resident macrophages, the main population of macrophages in the lesion is recruited from the blood in response to chemotactic products, as can be seen in extracellular matrix protein fragments, TGF-β, MCP-1 (protein 1 chemotactic for monocytes). [10] Based on the profiles of genic expression, macrophages can be classified as classically activated (M1 pro-inflammatory) and alternatively activated (M2 anti-inflammatory and pro-angiogenic). [11] These macrophages release growth factors, such as PDGF and VEGF, which are commonly necessary for

the triggering and propagation of new tissue in the lesioned area, since animals with a depletion of macrophages present defects in wound repair, conferring upon these cells a key role in the transition of the exudative stage to the proliferative stage within the tissue repair process. [12] Macrophages perform the functions of muscular debris phagocytosis, as well as the production and release of cytokines and pro-angiogenic, inflammatory, and fibrogenic factors, and of free radicals. [13] Moreover, the macrophages, upon secreting chemotactic factors, attract other inflammatory cells to the wound area. They also produce prostaglandins, which function as potent vasodilators, affecting the permeability of micro-blood vessels. Together, such factors cause the activation of endothelial cells. [14] These cells, according to Mendonça & Coutinho Netto, also produce PDGF, TGF beta, FGF, and VEGF, which stand out as the main cytokines capable of stimulating the formation of granulation tissue. [15]

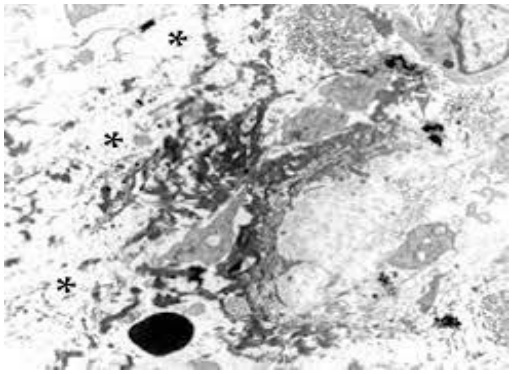


Figure 1: Accumula - tion of fibrin (asterisk) in the middle of the edema area in the extracellular matrix

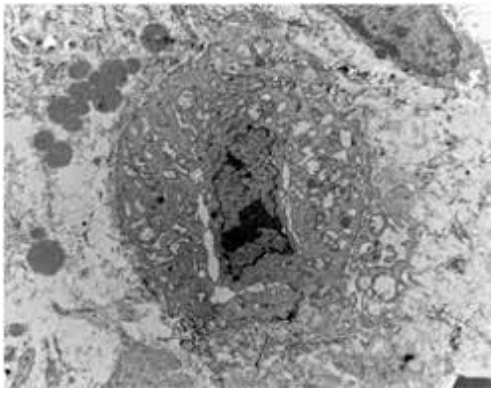


Figure 2: Electromi - crography of a leukocyte, with evident hydropic degeneration in the exsudative stage of the inflammatory process (Scanning Electron Microscopy – 7,000X).

PROLIFERATIVE STAGE

The aim of the proliferative stage is to diminish the lesioned tissue area by contraction and fibroplasia, establishing a viable epithelial barrier to activate keratinocytes. This stage is responsible for the closure of the lesion itself, which includes angiogenesis, fibroplasia, and reepithelialisation. These processes begin in the microenvironment of the lesion within the first 48 hours and can unfold up to the 14th day after the onset of the lesion. [14] Vascular remodelling prompts blood flow changes. Angiogenesis is a coordinated process, involving endothelial cellular proliferation, rupture and rearrangement of the basal membrane, migration and association in tubular structures, and the recruitment of perivascular cells. For some time, angiogenesis has been described as essential for diverse physiological and pathological conditions, such as embryogenesis, tumour growth, and metastasis. [16] The subsequent development of the blood vessels, according to Gonçalves et al., involves the production of collateral veins through two mechanisms: germination and cell division. [17] The resulting vascular plexus is remodelled to be differentiated in large and small blood vessels. The endothelium is then filled with both accessory and smooth muscle cells. The newly formed microvasculature makes it possible to transport fluid, oxygen, nutrients, and immune-competent cells to the stroma. [18] In addition to the active participation of endothelial and lymphocyte cells in this biological process, pericytes constitute a cell group stemming from the mesenchymal strain of smooth muscle cells, described many decades ago. [19] The aforementioned cells appear as solitary entities, sharing the basal membrane of blood vessels and endothelial cells (Figure 3). [20] The pericytes are lightly-coloured connective tissue cells containing long and thin cytoplasmatic processes in a position immediately outside of the endothelium of the blood capillaries and small venules into which the capillaries empty themselves. According to Ribatti et al., Charles Rouget, in 1873, was the first to describe such non-pigmented cells that presented

contractible elements. [21] However, these authors were unable to stain them.

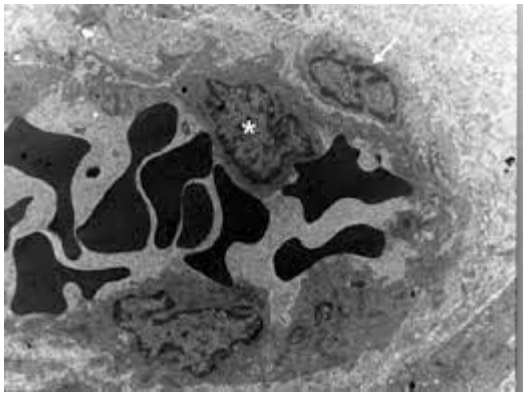


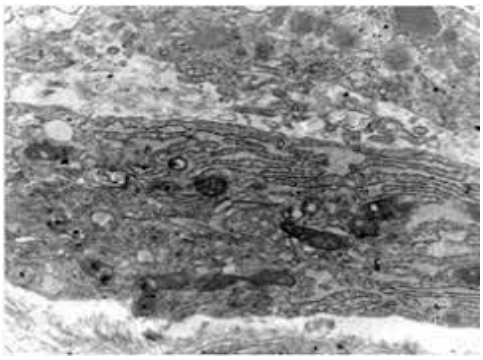
Figure 3: Electromicrography that illustrates the pericyte (arrow) in close contact with the endothelial cell (asterisk), sharing the basal membrane of this cell, which makes up the blood vessel wall (Scanning Electron Microscopy – 7,000X)

By contrast, Mayer, in 1902, using methylene blue stain, was able to view these cells, which were defined as pericytes by Zimmermann in 1923, due to their position on and around the blood vessels, with their processes wrapped around the basal surface of the endothelium. Through long cytoplasmatic extensions that stretch and surround the endothelial tube, the pericyte makes focal contact with the endothelium through specialized junctures. [22] Additionally, such a cell influences the stability of the blood vessel through the deposition of the matrix and/or the release and activation of signs that promote the differentiation or compliance of the endothelial cells. [23, 24] Pericytes are mural cells of micro-blood vessels involved in the basal membrane, which run continuously along the endothelial basal membrane. Some pericytes are most likely mesenchymal or progenitor cell strains that form adipocytes, cartilage, bone, and muscle. [22] There is substantive evidence that the pericytes retain a mesenchymal potentiality during adulthood that is enough to create not only fibroblasts, but also smooth muscle cells. [25] These cell elements can present pluripotent cell characteristics, which constitute an important "source of cell reserve." Though the plasticity of pericytes has yet to be fully studied, Farrington-Rock its potential for differentiation into osteoblastos, chondrocytes, fibroblasts, leiomyocytes, and adipocytes. [26]. This property seems to be quite pertinent to tissue repair, given that these cells can offer an overall contribution to the restocking of scar tissue. Granulation tissue begins to be formed approximately four days after the lesion. Its name is derived from the granular appearance of the recently-formed tissue, conferring this characteristic to the new stroma. According to Calin et al., the granulation tissue is formed through the following mechanisms: an increase in fibroblastic proliferation; collagenous and elastic biosynthesis, which creates a three-dimensional extracellular network of connective tissue; and the production of chemotactic factors and IFN-beta by fibroblasts. [27] Fibroblasts and endothelial cells express integrin receptors and, through these, invade the coagulation found in the lesion area. [28] For the tissue repair process to be understood, one must mention some particularities of the immune system, such as the participation of B lymphocytes and, more specifically, the multifunctionality of T lymphocytes. Morphologically, T lymphocytes are subdivided into functional populations: CD4 (auxiliary T lymphocytes) and CD8 (suppressor/cytotoxic T lymphocytes). The T CD4 cells are characterized based on their profiles of cytokine production, such as the subpopulation of Th1; producers of Il-2 and IFN gamma; Th2, which produces IL-4, IL-5, and IL-10; and Th17, which is characterized by the production of IL-17. 2 When a tissue lesion occurs, the repair process is modulated by the cell activity of the inflammatory response of the cells on the borders of the lesion (keratinocytes), as well as by the variety of cytokines and growth factors that influence migration, proliferation, and local cell differentiation. [29] The fibroplasia begins with the formation of granulation tissue, characterized by the proliferation of fibroblasts, the main agents responsible for the deposition of the new matrix (Figure 4). The main component of a mature connective tissue scar is collagen. Fibroblasts, producers of collagen, are recruited from the dermis of the border of the wound to synthesize this protein. The

formation of an intact basal membrane, between the epidermis and dermis, is essential for the reestablishment of its integrity and function. During this initial stage of repair, the type III collagen is predominant, synthesized by fibroblasts in the granulation tissue. [30]

Figure 4: Electromicrography presenting the part of the cytoplasm of a fibroblast that exhibits the hyperplasia of the endoplasmatic reticulum and mitochondria, illustrating an intense synthesis activity (Scanning Electron Microscopy – 12,000X)

Observed that the wound's contraction process begins at this stage, performed by the fibroblasts, which are rich in the alpha smooth muscle actin, known as myofibroblasts. Such cells, accumulated on the wounds' borders, execute contractive activities and contract the lesion's borders toward the centre. [27] Angiogenesis occurs in the extracellular matrix of the wound bed with the migration and mitogenic stimulation of the endothelial cells. [15] Such neovascularization accompanies the fibroblastic stage mentioned above. The good irrigation of the borders of the wound is essential for wound healing, as this allows for an adequate supply of nutrients and oxygen, as well as of immune-competent cells, to the stroma (Figure 5). [31,32] Parallel to all of the aforementioned events, the epithelial



coating cells, through the action of specific cytokines, proliferate and migrate from the borders of the wound in an attempt to close it, which is called reepithelialisation. The reepithelialisation of a wound by keratinocytes is performed by the combination of the proliferative stage with the migration of cells near the lesion. [14] The migration of keratinocytes occurs in the direction of the remaining skin of the lesion to its extremities. Epidermal cells of hair follicles quickly remove the coagulation and damaged stroma. [14] It is reported that the epidermal germ cells of the hair follicle, which create the hair bulb, serve as a reservoir for keratinocytes in the healing process. Approximately ten hours after the onset of the lesion, there is a development and stretching of the pseudopod projections of the keratinocytes, a loss of the extracellular matrix-cell and cell-cell contacts, a retraction of the tonofilaments, and the formation of actin filaments in the extremities of its cytoplasms.

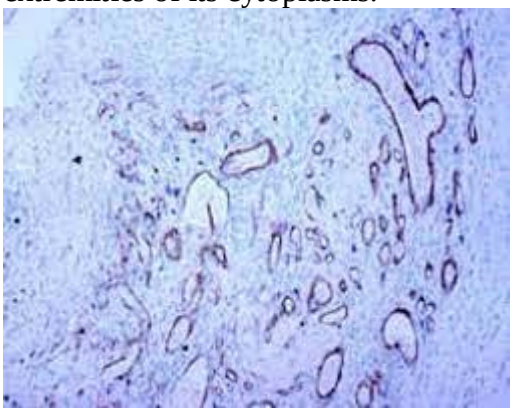


Figure 5: Neoangiogenesis demonstrated by an immunomarker with an anti-alpha smooth muscle actin antibody in rat skin, three days after inducing the standard skin wound (Immuno-histochemical - 100X)

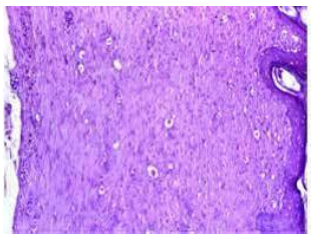


Figure 6: Fibroplasia area demonstrating the absence of skin annexes in the extracellular matrix and complete reepithelialization of the epidermis (hematoxylin-eosin – 100X)

When the migration ceases, possibly due to a result of the inhibition caused by contact, the keratinocytes are reconnected to the substrate and reconstruct the basal membrane. There is then the culmination of its differentiation process to generate the newly stratified epidermis (Figure 6) [14].

This stage is marked by the maturing of the elements with deep changes in the extracellular matrix and the resolution of the initial inflammation. As soon as the surface of the lesion is covered by a

monolayer of keratinocytes, its epidermal migration ceases and a new stratified epidermis with a subjacent basal lamina is re-established from the borders of the wound to its inner portion. (5) At this stage, there is a deposition of the matrix and subsequent change in its composition. [14] With the closure of the wound, type III collagen undergoes degradation, and synthesis of type I collagen increases. Throughout the remodelling, there is a reduction in the hyaluronic and fibronectin acid, which are degraded by cells and plasmatic metalloproteinase, and the growing type I collagen expression mentioned above is concomitantly processed.(17) It confirmed that, in this final stage, the collagen fibres become thicker and are placed in parallel, resulting in an enhanced tensile strength for the tissue.(33)The resolution stage is essential for the restoration of functionality and the "normal" appearance of the lesioned tissue.[1] This results from the low production of chemokines by anti-inflammatory cytokines, such as IL-10 or TGF-β1. The regulation of the collagen synthesis is controlled by a wide range of growth factors, such as TGF-β1 and FGF, which cause a strong effect upon the genic expression of this protein. During the maturation and remodelling processes, the majority of blood vessels, fibroblasts, and inflammatory cells disappear from the wound area due to emigration processes, apoptosis, or other unknown mechanisms of cell death. This fact leads to the formation of a scar with a reduced number of cells. At a later stage, the fibroblasts of the granulation tissue change their phenotype and begin to temporarily express the smooth muscle actin, which have received the specific name of myofibroblasts. [6, 27]

REMODELLING STAGE

The third phase of healing consists of remodelling, which begins two to three weeks after the onset of the lesion and can last for one year or more. The core aim of the remodelling stage is to achieve the maximum tensile strength through reorganization, degradation, and resynthesis of the extracellular matrix. In this final stage of the lesion's healing, an attempt to recover the normal tissue structure occurs, and the granulation tissue is gradually remodelled, forming scar tissue that is less cellular and vascular[3] and that exhibits a progressive increase in its concentration of collagen fibres (Figure 7).

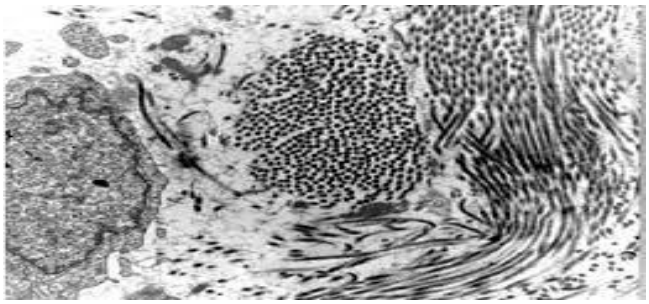


Figure 7: Electromicrography showing collagenous beams in different directions in the extracellular matrix, indicating the beginning of the process of fibroplasia, beginning on the seventh day after the onset of a skin wound, in an experimental model (Scanning Electron Microscopy – 12,000X)

This stage is marked by the maturing of the elements with deep changes in the extracellular matrix and the resolution of the initial inflammation. As soon as the surface of the lesion is covered by a monolayer of keratinocytes, its epidermal migration ceases and a new stratified epidermis with a subjacent basal lamina is re-established from the borders of the wound to its inner portion. [5] At this stage, there is a deposition of the matrix and subsequent change in its composition. [14] With the closure of the wound, type III collagen undergoes degradation, and synthesis of type I collagen increases. Throughout the remodelling, there is a reduction in the hyaluronic and fibronectin acid, which are degraded by cells and plasmatic metalloproteinase, and the growing type I collagen expression mentioned above is concomitantly processed. [17]

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temporarily express the smooth muscle actin, which have received the specific name of myofibroblasts. [6,27] Myofibroblasts, according to [27], acquire some contraction properties from smooth muscle cells, moving closer to the borders of the wound and becoming responsible for its contraction. In this manner, the referent cells present well-developed bands of contractible microfilaments composed of actin. These remain joined through communication junctures, and their cytoplasmatic filaments of actin are connected by integrin receptors to the fibronectin fibrils and to collagen I and III of the extracellular matrix. [1, 14]. In all of the processes cited above, it is important to emphasize that exogenous and endogenous factors can modulate such events and influence the healing process. More specifically, systemic disorders, such as diabetes, immunosuppression, venous stasis, as well as those resulting from external agents, such as the use of corticotherapy and smoking, can hinder the early closure of the wound. In addition to these complicating factors is the appearance of hypertrophic scars and keloids. [34]

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Obesity

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Ms. Gayatri H. Patil Assistant Professor.
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Introduction:[1,2,3]

Obesity is the one of the major diseases amongst chronic diseases in which excess body fat accumulated -in body or visceral organs. It is a metabolic disease. Due to imbalance between energy intake and expenditure of energy obesity occur. It gives rise to many health issues and now a days it become a main cause of disability and of death. Now become epidemic and not only found in adults but also in children. Obesity is risk factor in cardiovascular disease, Diabetes mellitus, many types of cancer and breathing disorders. The basic parameter for identification of obesity is BMI and increased waist circumference. In human measured by, body weight in kg divided by measured height square.

Epidemiology: [2]

According to World Health Organization (WHO), Obesity is one of the most serious chronic diseases and it give rise to many serious conditions. 2010, due to obesity 3.4 million deaths occur. 4% of people have lost their life and another 4% lived their life with disability. 2013, 42 million children under the age of 5 years found obese. 2014, 1.9 billion of people of age (18 and more than 18) found to be overweighted and of them 600 million found obese. If this condition is ongoing then by 2030, 3.4 billion people will find overweighted and obese, which is over 60% of world's population.

Types of obesity and risk of complications:[1]

Classification	**BMI**	**Risk of complications**
Underweight	< 18.5	Low
Normal range	18.5 to 24.9	Average
Overweight	>25	--
Pre-obese	25.0-29.9	Increased
Obese class 1	30.0-34.9	Moderate
Obese class 2	35.0-39.9	Severe
Obese class 3	>40	Very severe

Signs and symptoms:[3]

i) Excessive body fat
ii) Shortened breath
iii) Excessive sweating
iv) Skin rashes (due to folds on skin)
v) Pain at joints and fatigue
vi) Psychological issues
vii) Swelling and varicose veins in lower limbs
viii) Snoring
ix) High cholesterol levels (increase in lipid profile)
x) Accumulation fat
xi) Weight gain
xii) Increase in BMI

4) Etiology:[1,2]

i) Age
ii) Overacting
iii) Pregnancy
iv) Lack of exercise and lifestyle
v) Family history
vi) Medications
vii) Hormonal imbalance
viii) Poor sleep
ix) Stress

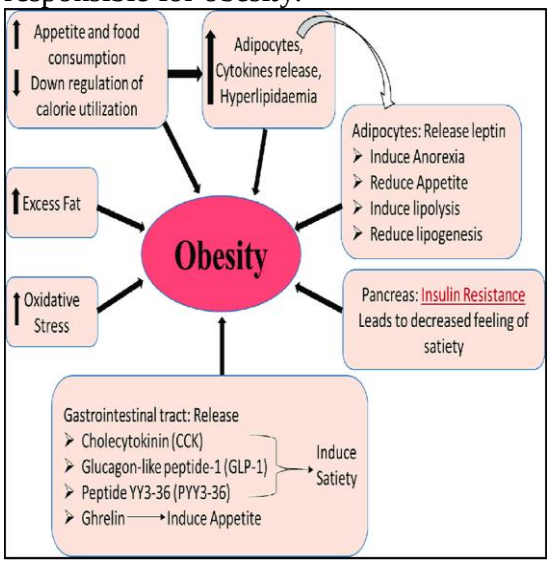
Risk factors:[2]

i) Lack of physical activity and exercise and high energy intake
ii) Smoking
iii) Socio-economic status
iv) Environment
v) Unhealthy diet
vi) Genetics
vii) Age
viii) Various diseases (joint pain, diabetes, cardiovascular diseases)
ix) Secretions of adipokines

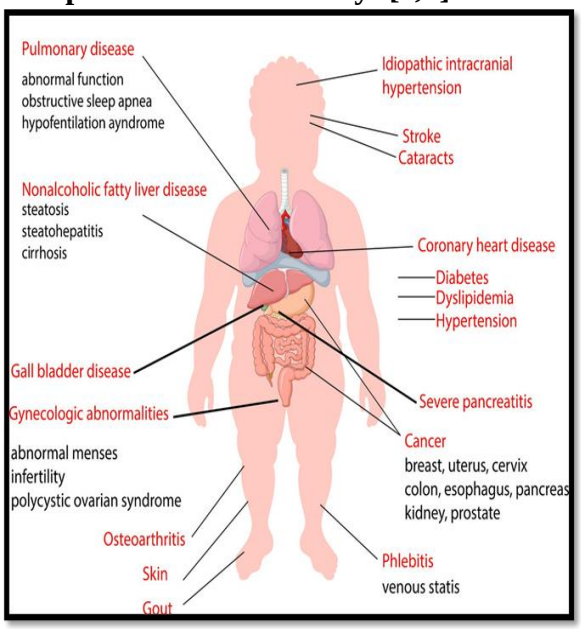
Pathophysiology:[1,3]

Multiple hormones are involved in the regulation and pathophysiology of obesity, including gut-related hormones, adipokines and others. Ghrelin is a

circulating peptide hormone derived from the stomach; stimulates appetite. Several hormones, collectively referred to as adipokines, are produced by the adipocytes. The key secretory products are tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), leptin and adiponectin. Leptin acts as a dominant long-term signal responsible for informing the brain of adipose energy reserves.. These behavioural and environmental factors lead to alterations in adipose tissue structure (hypertrophy and hyperplasia of adipocytes, inflammation) and secretion (e.g., adipokines). Oxidative stress also responsible for obesity.



Complications with obesity: [1,2]



Diagnosis: [2]

Diagnosis of obesity can be done by,

i) Liver function studies
ii) Thyroid function test
iii) Fasting glucose
iv) Lipid profile
v) BMI

8) Prevention:[4]

i) Healthy eating behaviour.
ii) Regular physical activity.
iii) Limiting unhealthy foods.
iv) Maintaining healthy habits.

Treatment:[2]

Classification	Examples
HMG-COA reductase	Atorvastatin, lovastatin, Fluvastatin, simvastatin
Bile acid binding resins	Cholestyramine, colestipol
Inhibitors of cholesterol absorption	Ezetimibe
Niacin	Nicotinic acid
Fibric acid derivatives	Fenofibrate, gemfibrozil, clofibrate

Non-pharmacological treatment:[5]

i) Balanced deficient diet depending on patient's weight
ii) 30-60 minutes of physical activity daily
iii) Changing bad habits
iv) Weight-loss/ weight management programmes.
v) Weight loss devices
vi) Bariatric surgery.
vii) Special diets: Calorie-restricted diets, intermittent fasting etc.

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Moyamoya Disease: A Review

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ABSTRACT:

Moyamoya disease is a rare chronic cerebrovascular disease first identified in the 1960s mostly affects people in Japan. It mainly affects the large blood vessels in the cerebrum that often results in haemorrhagic strokes, seizures, migraine, etc. Only imaging methods can be used to diagnose the disease after symptoms develop. Till date there is no treatment which can cure the disease completely. Although surgery can prevent future strokes but can't help in getting rid of the disease completely. The current study focuses on the disease analysis and the various methods for its diagnosis and management.

INTRODUCTION:

Moyamoya disease (MMD) is a rare disease first identified and described in the 1960s. [1] It is a chronic cerebrovascular condition that causes a collateral vascular network to grow at the base of the brain due to gradual stenosis of the Internal Carotid Artery's (ICA) terminal segment and the circle of Willis. [2] The disease is named after "Moyamoya", a Japanese word meaning puff of smoke as per the cerebral angiography of a diseased person. The main affected areas are the proximal sections of the surrounding middle cerebral artery and anterior cerebral artery, as well as the terminal segment of the intracranial internal carotid artery. In the area of the stenotic or occlusive arterial lesions, a frail compensatory vascular collateral network develops. [3] It is a progressive idiopathic disease that blocks the terminal internal carotid arteries, causing repeated strokes. [4]

INCIDENCE AND PREVALENCE:

MMD reportedly exhibits regional and ethnic traits. As compared to Europe, America, Africa, and Latin America, Asia has a greater incidence of MMD. Japan has the greatest incidence of MMD and a reliable system for registering case information also exists. [5] A survey conducted in 1995 in Japan found that the prevalence of MMD was roughly 3.16/100,000, while the incidence was estimated to be 0.35/100,000. [6] An additional study conducted in 2004 revealed a significant increase in the number of patients, with an estimated incidence of 0.54 per 100,000 people and a prevalence of 6.0 per 100,000 people in 2003. [7] There have also been numerous reports of MMD outbreaks in other southeast Asian nations like China and South Korea. According to a population-based study conducted across the entire country of South Korea, there were 8,154 MMD patients in 2011, and the incidence rose from 1.7 to 2.3 cases per 100,000 people between 2007 and 2011. [8]

SIGNS AND SYMPTOMS:

Transient ischaemic attack, ischemic and hemorrhagic strokes, seizures, headaches, and cognitive impairment are some of the clinical manifestations of MMD. Each symptom's frequency varies depending on the patients' ages. [9] The most significant clinical symptom of MMD is an ischemia episode. [10] Around half of adult patients with MMD have intracranial haemorrhage, and the other half have ischemic issues. Most children with MMD experience ischemic consequences, such as transient ischemic stroke and cerebral infarction. [11] The main causes of symptoms are alterations in cerebral blood flow brought on by ICA stenosis (ischemia) and the brittleness of the compensatory capillary collaterals (hemorrhage). [12]

PATHOPHYSIOLOGY:

The hyper-proliferation of vascular wall cells, active angiogenesis, matrix buildup, irregular undulation of the internal elastic laminae, medial thinness (such as an attenuation of media), and a reduction in the outer diameter are the key pathogenic alterations of the stenotic segment in MMD. [13-18] Recent neuroimaging techniques have shown constrictive

remodelling (e.g., the narrowing of the arterial outer diameter) in affected segments and concentric enhancement of the symptomatic segments in patients with MMD. [19-22] These techniques include three-dimensional (3D) Constructive Interference In Steady-State (CIISS) MRI and high-resolution MRI studies. Regardless of the presence or severity of symptoms, the majority of patients with adult-onset MMD (90.6%) demonstrated long-segment concentric enhancement of the distal ICA and/or middle cerebral artery on a high-resolution MRI. The results of prior pathology reports that demonstrated intimal hyperplasia and medial thinness are compatible with the high-resolution MRI findings. [23, 24]

DIAGNOSIS:

Computed Tomography

The presence of cerebral cortical atrophy, most frequently in the frontal lobes, numerous infarcts, and intracranial haemorrhage are among the non-specific CT manifestations of moyamoya disease. In the basal ganglia, the aberrant parenchymal collateral arteries are shown as numerous serpiginous low attenuation patches that become more evident following intravenous contrast agent injection. Although the symptoms are strongly suggestive, they do not give proof that moyamoya disease exists.[25,26]

Figure 1 : Computed Tomography

Magnetic Resonance Imaging

With increased accessibility, MRI has frequently replaced other imaging modalities as the first choice for diagnosing neurological diseases because it combines the benefits of a noninvasive, radiation-free imaging method with superior grey/white matter distinction. Just lately has magnetic resonance been studied for its potential in the diagnosis and monitoring of moyamoya illness.[27] Using normal spin-echo techniques, it was possible to see the majority of the disease's angiographic characteristics, such as the internal carotid artery's constriction and occlusion, dilated pericallosal collaterals, and parenchymal alterations brought on by the arterial occlusion. The basal ganglia collateral vessels can best be seen through imaging in the coronal plane. [28, 29]

Figure 3 : Magnetic Resonance Imaging (MRI)

Electroencephalogram

The electroencephalogram (EEG) can show how the brain network functions and the overall electrophysiological effects. [30] It is a noninvasive technique with excellent temporal resolution that is able to capture neural activity in MMD patients. [31] EEG is helpful for assessing brief neurological events in MMD to differentiate seizures from epileptiform alterations, according to a prior study. [32] In MMD, temporary cortical depression frequently leads to postoperative transitory neurological impairment. [33] EEG can pick up on this as a low amplitude arrhythmic slowdown in the affected hemisphere. [34]. Also, several investigations have discovered a correlation between the clinical results in MMD and focal ischemia episodes and epileptic waves recorded on an EEG. [35, 36]

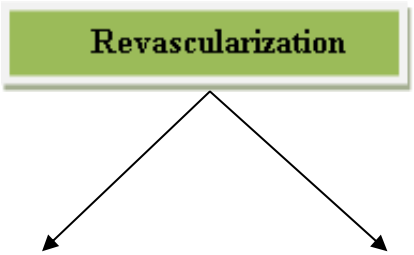
Figure 2: Electroencephalogram

TREATMENT:

The management of moyamoya disease has been discussed in terms of a variety of surgical revascularization approaches. [37] Since cerebral ischaemia is the main symptom of paediatric moyamoya disease, these are mostly useful in treating it. Although it is theoretically favourable to delay the formation of the delicate moyamoya veins using early revascularization procedures in order to prevent repeated haemorrhage, surgery has not been demonstrated to be beneficial in adults. [38]

Surgical revascularization

The primary objective of surgical revascularization is to improve cerebral blood flow (CBF) and replenish reserve capacity in order to prevent cerebral infarction. Recurrent clinical symptoms brought on by either1) apparent cerebral ischemia or 2) decreased regional CBF, vascular responsiveness, and reserve in perfusion investigations are generally recognised as indications for revascularization. [39]



Direct Revascularization

- Improvement in flow occurs right away following surgery after donor and recipient arteries successfully anastomosed.[40]
- Though technically challenging, this treatment calls for a skilled surgeon. A direct bypass may be possible depending on the Superficial Temporal Artery's (STA) and cortical arteries' vascular sizes.
- Most cortical arteries in individuals with advanced MMD have shrunk to a tiny caliber, and their vessel walls are typically more brittle.
- Another significant issue causing neurologic impairment after direct bypass surgery is post-operative hyper perfusion syndrome.[41-45]

Indirect revascularization

- Due to the recipient artery's tiny size, direct bypass might be a challenging treatment for young pediatric patients or adult patients with advanced MMD.
- Fortunately, indirect bypass employing a variety of connective tissues has been successful in these situations, probably as a result of the disease's tendency to encourage the creation of leptomeningeal collaterals on its own. [46,47]
- Indirect revascularization is easier to do than direct surgery is one of its benefits.
- This reduces the duration of the procedure, which is crucial for avoiding difficulties.
- In addition, indirect revascularization is rarely followed by post-operative hyper perfusion syndrome.
- The improvement in cerebral blood flow, however, requires longer time because connective tissue revascularization does not occur right once.[48]

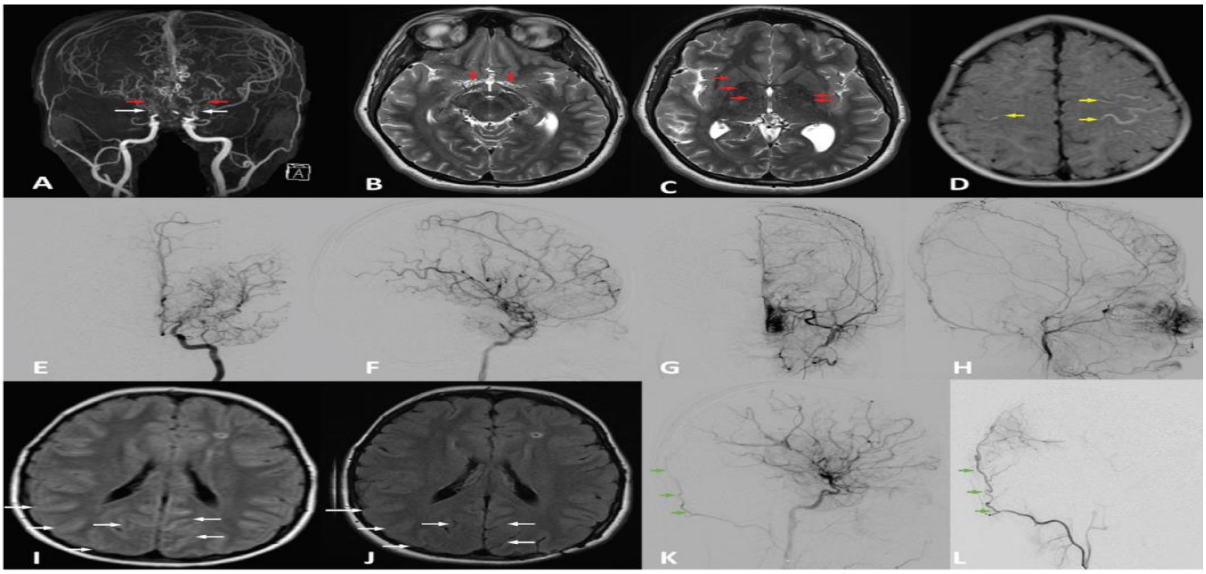


Figure 4 : Radiographic imaging modalities for diagnosis and follow-up of moyamoya It includes magnetic resonance angiogram (MRA) coronal view (A) demonstrating bilateral stenosis and occlusion (white arrows) of the internal carotid artery (ICA) terminus, M1 segment of middle cerebral artery (MCA), and A1 segment of anterior cerebral artery (ACA). Notice extensive proliferative changes of the lenticulostriate arteries bilaterally (red arrows). Axial brain MRI T2WI, at level of basal cisterns (B) and basal ganglia (C) demonstrate void signals (red arrows) of moyamoya collaterals. Axial brain MRI FLAIR sequence (D), showing ivy sign bilaterally (yellow arrows). Anteroposterior (E) and lateral (F) digital subtraction angiogram (DSA) of the left ICA show stenosis of the terminal ICA and thread-like appearance of the M1 and A1 segments, with reconstitution of MCA and ACA candelabra by lenticulostriate collaterals; most consistent with Suzuki stage III. Anteroposterior (G) and lateral (H) DSA of the left external carotid artery (ECA) shows intrinsic ECA to ICA transdural collaterals from middle meningeal and superficial temporal artery. Atypical moyamoya with posterior cerebral disease (I-L): preoperative (I) and postoperative (J) FLAIR sequence showing preoperative ivy sign and its disappearance following pial synangiosis (white arrows). Preoperative lateral DSA of left ECA (K) and postoperative lateral DSA of left occipital artery (L) following pial synagniosis using the occipital artery as a donor, demonstrating ingrowth of collaterals from the occipital artery. Notice the increased size of the donor artery (green arrows) compared to the preoperative DSA

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