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"A REVIEW OF VISHAMJWARASAMPRAPTI IN BHEL SAMHITA WITH SPECIAL REFERENCE TO CYTOKININ RELEASE SYNDROME. (CRS)"

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Abstract: -

Vishamjwara is the special type of Jwara which is explained in all classical text of Ayurveda. Vishamjwara is classified according to its onset of duration and its clinical presentation regarding specific sites. Bhel samhita is one of the ancient ayurvedic text. Maharshi "Bhel" is one of the six students of Atreya Punarvasu. Some chapters of Bhelsamhita are missing but remaining chapters are very informative. Vishamjwara chikitsa is one of them. Bhel samhita elaborated Vishamjwara samprapti according to involvement of specific dosha-dushyas on successive days which is very unique and different explanations than other ayurvedic samhita. These vishamjwara samprapti lakshanas shows resemblance to cytokinin release symptoms which occur in malaria.So, Bhel samhita provide a new aspect regarding cytokine release syndrome (CRS) in terms of ayurveda.

Key words: -Bhelsamhita, vishamjwara samprapti, lakshanas, malaria, CRS.

Introduction: -In Brihat-trayi and Laghu-trayi, vishamjwara is explained as special type of jwara indetail regardingnidan,samprapti and its types. But in Bhel samhita 'Bhelacharya' had mentioned unique and different samprapti,lakshanas of vishamjwara**.**

Bhel samhita is composed by 'Bhel' whoone of the six disciples of Punarvasu atreya. Itis a contemporary of 'Agnivesha.'Samprapti lakshanas mentioned in Bhel samhita shows resemblance to pathophysiology of malaria with cytokinin release syndrome in modern literature. So here, literatual study of vishamjwara samprapti lakshanas in Bhel samhita is corelated with cytokine release syndrome.

Material and methods: -This study is based on literatual review of classical information, published research work and modern literature. The possible correlation has been made between collected information and has been presented in systemic way.

Vishamjwara in Brhuttrayi and Laghutrayi: -Jwara is considered as the king of all diseases with many complications. jwara-prabhavreflects on the birth and death of human beings. Mythologically jwara develops due to anger of Lord Shiva. Jwara is the manifestation of "Dehaindriya manah-stapah" with root causesdue torasavaha srotodushti.

Vishamjwara is the special type of jwara having characteristic of vishama-vegijwara explained by Madukoshkar.[1]According to Vaghbhatacharya it is due to "vishamarambha kriya kaal" means irregularity in the onset, progress, and duration of the diseases. "Muktanu-bandhitwam"is another peculiarity whereas the sudden onset(on and off) of fever occurs.[2]

Nidana: -Vishamjwara occur due to both 'Nija'(doshaj) and 'Agantuja' (external infection/pathogenic) factors.Nija doshas indicated by the presence of 'alpa bala doshas' due to previous jwara's incomplete treatment or relapsing fever due to lack of 'apunarbhava chikitsa'.[3]

Sometimes history of previous jwara cannot be traced. Vaghabhatacharya clearly mentioned that the person who recently relieved from the disease, still continuedmithya ahara and vihara, then alpa bala doshas become powerful and get strain from dushyas.[4] As vishamjwara is categorized under 'Mala kala bala abalat.' Its manifestation depends on the strength of dosha at particular time.[5]

According to Sushrutaharya, vishamjwara is due to agantujafactors (external cause) like 'Bhutabhishanga'.[6] Now a days, Aacharya Gananatha Sen was interpreted these "Bhuta" as microbes.[7]According to'Charakacharya',vishamjwara alwaysmanifests as 'Sannipataja jwara'.[8] So, all the causative factors of sannipatika jwara are considered as nidan of vishamjwara.[9]

Samprapti: -Basically, doshas in low power get strength due to mithya ahara& vihara factors and invades the dhatus to produce symptoms.[10] Doshas also get strength due to their own period for twenty-four hours. i.e., during prakrit gati of doshas. When doshas bala is ksheena (low power), they lurk in rasadi dhatu. They produce mild fever, exhausts, debility, heaviness, inactiveness, and discoloration.[11]So, when doshas, dushyas, and kala are favorable then only symptoms of vishamjwara are produced.It is all compared to dormancy of seeds.[12]Vata dosha plays important role in the acute manifestation of vyadhi and due to which vegavastha (phase of fever) occur.[13]

Types according to sites of manifestation: -Generally, five types of vishamjwara are explained santata, satata, anyedyushka, tritiyaka and chaturthaka.[14]'Charakacharya' and 'Madhavakar' mentioned the involvement of exact dushyas in specific type ofvishamjwara.Hence, insantata, satata, anyedyushka, tritiyaka and chaturthaka jwara, the involvement of rasa, rakta, mamsa, meda, and asthi-majja occurs respectively. [15] According toSushrutacharya, there is involvement of different sites of 'kapha' dosha in specific vishamjwara. Doshas travel from particular kapha sthana to aamashaya.Timerequires for movement of doshas reflect as pattern ofvishamjwara. Aamashaya, urah, kantha, shira, and sandhi are involved respectively in vishamjwara. [16]

Santata Jwara: -It has 12 ashraya bhava. It is a continuous type of fever persisting for 7, 10, or 12 days depending on dosha's dominancy.

Satata Jwara: -Fever rises twice in 24 hours.

Anyedyushka: - Fever rises only once in a day.

Tritiyaka: - Fever appear on third day.

Chaturthaka: -Fever appear on fourth day.

In Charaka samhita tritiyaka jwara is sub classified as depending on dosha dominancy and afflicted region. Vata pittaja –shiro-grahi, (head), Pitta kaphaja – trika-grahi (lumbar region) and Vata kaphaja – prushtha grahi (back region).[17]

Chaturthaka jwara is subclassified as 'Shlaishmaika' and 'Vatika' starting from calf and head region respectively. Chaturthaka viparyaya is explained by Charakacharya.Itoccurs due to tridosha, which get lodged in asthi and majja dhatu and fever remains for two days then one day remission, it appearsagain.[18]

In Sushrutasamhita total 12 types of vishamjwara are explained. It includes regular 5 types as well as 'Viparyaya' of all types and aupatyka, madyotha, pralepaka and vata-balasaka. Out of them Sushrutacharya explains three types according to duration of fever throughout the 24 hours.[19]

Tritiyaka Viparyaya occur on second day and remission occur on first and third day. In'Anyeduska viparyaya'fever occur during five kaal and remission occur during onlyone kaal. Means remission of fever occur for four hours for 24 hours. In satata jwara,'Viparyaya' fever occur for four hours and remission for eight hours throughout 24 hours.

According to Sushrutasamhita,vata-balasaka and pralepaka jwara are considered as chronic stage of vishamjwara. Madhavnidan explains some more types,depending on the site of lodgment of vitiated vata and pitta dosha, Patients feels hotness and coldness in the body. It may resemble to 'Ardha-narishwara' or 'Narasimha' idol.[20] Sheetapurvaka and dahapurvaka jwara are explained in the context of vishamjwara.If vitiated vata, kapha resides in the skin, means in the shakha, then patient shows chills with rigors before fever. i.e.,sheeta purvaka jwara.If vitiated pitta resides in the shakha part, then patient shows burning sensation before fever i.e.,dahapurvaka jwara.[21]

Ashtanga Sangraha mentioned 'Ratrika jwara' due to sama kapha, samavata and hina pitta, and 'Purva ratrika jwara' which occur during day due to hina kapha. [22]Kashyap Samhita mentioned 7 types of vishamjwara. Also explained that, upward direction of 'Tejas' (pitta) causes obstruction of srotas in the head region, which manifest as hotness in head region and coldness in the extremity.[23]

Vishamjwara in Bhel samhita: -In Bhel samhita,'Jwara nidan' sthana is not available. But in 'Jwara chikitsa' sthana, it is clearly stated that vata dosha is responsible for vegavastha in jwara.[24]

In Charaka samhita, we get 'Ushna'jwara as 'Vata-pittatmaka' jwara and 'Sheet'jwara as 'Vata kaphatmaka' jwara. Even in Madhavnidan, we got 'Sheeta purvaka'jwara and 'Daha purvaka'jwara references.But in Bhel samhita clearly mentioned the state of doshas and how samprapti of 'Sheet' jwara and 'Ushna' jwara occur alternatively because of vata dosha. Aggravated vata dosha vitiates the pitta from its twakgata site and invades the roma-kupa to produce the symptoms of 'Sheet Prachiti' i.e.,chills and rigors. Then vitiated Pittanubandhi vata dosha causes liquification of kapha which ultimately increases 'Jala'mahabhoota adhikya, which again dries up vitiated pitta and again shows the symptoms of daha i.e., fever. Ultimately it all reflects pathogenesis of 'Sheeta purvaka'jwara in vishamjwara.[25]

Nidana: - Bhel samhita elaborated vishamjwarain separate chapter. Bhelacharya mentioned the different opinion of 'Acharyas' regarding the genesis of vishamjwara. As, due to vata,

pitta, kapha, Sannipata, bhoota and graha-badha. Vishamjwara occur as vatajanya vikara.It reflects the opinion of Sushrutacharya, according to him,vata dosha is very important without it vishamjwara samprapti cannot be manifested.'Pittajanya'vishamjwara indicate dominancy of pitta dosha which manifest as dahapurvaka jwara. 'Shleshma-janya' jwara indicates dominancy of kapha dosha as in 'Sheeta purvaka'jwara explained in Madhavnidan.Sannipataja vishamjwarait reflects the Charakacharya opinionthat vishamjwara are often sannipataja.[26]

Bhoota-sambhava denotes agantuja factors like 'Bhutabhishangaja'. Also mentioned the 'Graha-badha' which reflects the 'Abhicharaja' and 'Abhishapaja' types of agantuja jwara.After mentioning all views, Bhelacharya clearly explained his opinion that vishamjwara is always sannipataja.[27]

Samanya samprapti of vishamjwara: - 'Pakvashayastha'vata get aggravated and invade the asthi-majja dhatu and vitiate the kapha-pitta and produce vishamjwara. Here, we notice that Bhelacharya elaborated the vataprakopakasite as'Pakvashaya' where genesis of vata dosha take place after sara-kitta vibhajan. So, pakvashayastha vata dushti mainly vitiation of apan vayu by aharaja factor which plays an important role in samprapti. Involvement of asthi-majja dhatu in samprapti indicate dominancy of vata dosha due to their 'ashraya ashrayi'bhava. So, in dosha samanya samprapti ghataka,indicate vishamjwara as madhyammargashrita and krichra sadhya vyadhi.

Types: -Three types of vishamjwara are stated asanyedyushka, ekantarita and chaturthaka. Satata and santata types which are afflicted to rasa and rakta dhatu respectively are not mentioned. But chaturthaka jwara is mentioned as difficult to treatment.[28]

Rupa-avastha: - Bhelacharya specifically mentioned the sequence of vishamjwara manifestation. On first day vitiation of asthi-majja dhatu occur. On second day vitiation of rakta and mamsa dhatu takes place& on third day, vitiation of kapha and vata dosha takes place. While on fourth day, vitiation of pitta dosha take place.[29]

It's a very different opinion and regarding manifestation and pathogenesis of vishamjwara.Other symptoms of vishamjwara are not mentioned in Bhel samhita. But we can assume the symptoms as treating the vishamjwara as 'Sannipatika'jwara.As Bhelacharya and Charakacharya are both are the students of Punarvasu Atreya.Their opinion may show some similarities rather than Sushrutacharya opinion.

Charak samhita references – In Charaka samhita, total 13 types of sannipatikajwara are explained. But here we consider the symptoms caused by greater discordance of vata dosha than other doshas.

Vatolbana kapha and pitta hina symptoms include – 1. Sandhyasthi shirashoola – piercing joint pain, 2. Pralap – delirium, 3. Gaurav – heaviness in the body, 4. Bhrama – stupor ness, 5. Trishna – thirst,Kantha shushkata – throat dryness. [30]

Vatolbana kapha madhya pitta hina symptoms include –1. Shiroruka –headache, 2. Vepathu – trembling, 3. Shwasa –dyspnea, 4. Pralap –delirium,5. Chhardi –vomit,6. Arochaka – Indigestion. [31]

Vatolbana pitta madhya kapha hina– 1. Shwasa –dyspnea, 2. Pratishyaya –coryza, 3. Mukha shosha –dryness of mouth, 4. Atiparshwa ruka –mid-axillary pain. [32]

Madhavnidan references – Madhavnidan mentioned 'Visphuraka'as 'Vatolbana sannipataja'lakshanas are as follows (Ma. Ni. Madhu kosha.)– 1. Trishna –thirst, 2. Glani – stuporness, 3. Parshwa ruka –latero-thoracic pain. 4. Drishti Kshaya –blur vision, 5. Pindikodveshtan –calf pain, 6. Daha –burning sensation, 7. Urasada –thoracis pain, 8. Bala kshaya –emaciated power, 9. Sa-rakta mala pravrutti –malena, 10. Sa-rakta mootra pravrutti – hematuria, 11. Shoola –paining, 12. Nidraviparyaya –day time sleep, 13. Bastivedana – renalunit pain, 14. Nirbhidyate Gudam – cutting pain at anal region, 15. Hikka –hiccup,16. Murccha –fainting, 17. Vilap –mourning.

After compelling all above symptoms, we can easily sort out specificdosha and dhatu dushti lakshanas which occur in vishamjwara according to Bhel samhita.

Bhel samhita references are as follow.

On first day – Asthi-majja dhatu dushti occurs with symptoms of 1.Sandhyasthi shiraShoola –joints pain with headache, 2. Shiro-ruka –compress headache, 3. Vepathu – trembling/quacking, 4. Atiparshwa ruka –thoraco mid-axillary pain, (effusion.), 5. Bhrama – vertigo, 6. Pralap –delirium, 7. Glani –debility/fatigue of body, 8. Vilap –mourning, 9. Shoola –pains.

On Second day – Rakta-mamsa dhatu dushti occur with symptoms of 1.Daha –burning sensation,2. Sa-rakta Mala Pravrutti –malena,3. Sa-rakta mootra pravrutti –hematuria,4. Pindikodveshtan –calf muscles pain,5. Basti vedana –renal unit pain,6. Gudavedana –anal region paining, 7. Shoola –pains.

On Third day – Kapha-vayu dushti occur with symptoms of 1.Gaurav –heaviness,2. Pratishyaya –coryza,3. Hikka –hiccup,4. Shwasa –dyspnea, 5. Urah-sada –chest pain,6.Bala kshaya –emaciated force,7. Trishna –thirst,8. Kantha shushkata –soreness of throat, 9. Mukha shosha –dryness in mouth,10. Nidraviparyaya – day time sleep, night awake.

On Fourth day –Pitta dushti occur with symptoms of 1.Daha –Burning sensation, 2. Jwara –fever, 3. Drishti Kshaya –blur vision,4. Sa-rakta mala pravritti –malena,5. Sa-rakta mootra pravritti –hematuria,6. Trishna –thirst,7. Kantha shushkata –dryness of throat,8. Murccha – fainting.[33]

Modern view in malaria – Vishamjwara is correlated to 'Malaria' in modern science with its typical symptoms like fever with chills.Malaria is caused by the protozoan *Plasmodium*, transmitted to humans by *Anopheles* mosquitoes. The most dangerous of the plasmodia infecting humans is *Plasmodium falciparum*. Most of the clinical signs of this disease are caused by the parasite at stages in which it multiplies asexually in red blood cells.

Life cycle of 'Malarial parasite' – The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host.

Then Sporozoites infect liver cells and mature into schizonts, which rupture and release merozoites i.e. (**exo-erythrocytic schizogony**).The parasites undergo asexual multiplication in the erythrocytes **(erythrocytic schizogony).** Merozoites infect red blood cells. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites. Some parasites differentiate into sexual erythrocytic stages (gametocytes). The gametocytes, male (micro-gametocytes) and female (macro-gametocytes)are ingested by an*Anopheles*mosquito during

blood sucking. The parasitesmultiplication in the mosquito is known as the **sporogony cycle**. While in the mosquito's stomach, the micro-gametes penetrate the macro-gametes generating zygotes. The zygotes in turn become motile and elongated (ookinetes) which invade the midgut wall of the mosquito where they develop into oocysts. The oocysts grow, rupture, and release sporozoites, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle. At the completion of the schizogony within the red cells, each cycle lasting 24-72 hours depending on the species of the infecting parasite. All the clinical features of malaria are caused by the erythrocytic schizogony in the blood.[34]

Pathophysiology of Malaria – The growing parasite progressively consumes & degrades intracellular proteins, principally haemoglobin, resulting in formation of the 'malarial pigment' and haemolysis of the infected red cell.This also alters the transport properties of the red cell membrane, and the red cell becomes more spherical. The rupture of red blood cells by merozoites releases certain factors and toxins (such as red cell membrane lipid, glycosyl phosphatidyl inositol anchor of a parasite membrane protein), which could directly induce the release of cytokines such as TNF and interleukin-1 from macrophages, resulting in chills and high-grade fever. This occurs once in 48 hours, corresponding to the erythrocytic cycle.

In the initial stages of the illness, this classical pattern may not be seen because there could be multiple groups (broods) of the parasite developing at different times, and as the disease progresses, these broods synchronise, and the classical pattern of alternate day fever is established.It has been observed that in primary attack of malaria, the symptoms may appear with lesser degree of parasitaemia However, in subsequent attacks and relapses, a much higher degree of parasitaemia is needed for onset of symptoms. The first symptoms of malaria after the inoculation of parasite, when the sporozoites undergo schizogony in the liver are called the ***primary attack.*** It is usually atypical and may resemble any febrile illness.

As the disease gets established, the patient starts getting relapse of symptoms at regular intervals of 48-72 hours. The primary attack may spontaneously abort in some patients and the patient may suffer from relapses of the clinical illness periodically after 8-10 days owing to the persisting blood forms of the parasite. These are called as ***short-term relapses (recrudescence).*** Some patients will get ***long term relapses*** after a gap of 20-60 days.

All these are due to the reactivation of the hypnozoites in the liver in case of vivax and ovale malaria. In falciparum and malariae infections, and relapse symptoms can occur due to persistent infection in the blood. All these compared to alpa dosha which lurks in srotas and then after achievingkala, dosha dushya-bala symptoms occur.

Different parasites and their relapsing period– In Plasmodium vivax or Plasmodium ovalemalaria, typical pattern of fever recurs once every 48 hours and this is called as *Benign Tertian malaria.* In Plasmodium. malariae infection, the relapses occur once every 72 hours and it is called **Quartan malaria**.In Plasmodium Falciparum occur with periodicity of twenty-four hours and it's called **'Quotidian'** fever.

Typical features are: - The febrile episode includes1. cold stage, 2. hot stage and 3. sweating stage.

It starts with shaking chills, usually at mid-day between 11 a.m. to 12 noon, and this lasts from 15 minutes to 1 hour (the cold stage), followed by high grade fever, even reaching above 106^0 F, which lasts 2 to 6 hours (the hot stage). This is followed by profuse sweating and the fever gradually subsides over 2-4 hours. These typical features are seen after the infection gets established for about a week. The febrile paroxysms are usually accompanied by headaches, vomiting, delirium, anxiety and restlessness and disappears with normalization of the temperature.

Symptoms of Malaria are: - It includes systemic manifestation like headache, bodyache, backache,joints pain, weakness, acute abdomen, vomiting, diarrhoea, pallor puffiness of eyelids, jaundice, chest pain and cough. In sever conditions like cerebral malaria caused by Plasmodium falciparum shows symptoms like altered sensorium, convulsion, coma.[35]

Role of Cytokinin in pathophysiology of Malaria: - The newly developed merozoites are released by the lysis of infected erythrocytes and along with them, numerous substances, such as red cell membrane products, malarial pigment, and other toxic factors such as Glycosylphosphatidylinositol (GPI.) are also released into the blood. The GPI. activate macrophages and endothelial cells to secrete cytokines and inflammatory mediators such as tumour necrosis factor, interferon-γ, interleukin-1, IL-6, IL-8, macrophage colony-stimulating factor, and lymphotoxin, as well as superoxide and nitric oxide(NO.)

In addition to these factors, the plasmodial DNA is also highly proinflammatory and can induce cytokinesis and fever.The cytokines,tumour necrosis factor, interleukins, interferon-γ, and nitric oxide involved in pro-inflammatory cascade and act as double-edged swords in the pathogenesis of malaria. Cytokines act as homeostatic agents and an early pro-inflammatory cytokine response helps in limiting the infection, with the cytokines inhibiting the growth of malarial parasites in lower concentrations. On the other, failure to down-regulate this inflammatory response results in progressive immune pathology, leading to complications.Excessive levels of cytokines can lead to structural changes in the infected red cells and the resulting in cytoadherence means increase in their rigidity and adhesiveness to the capillary endothelium.

The infected red cells also adhere to the uninfected red cells, resulting in the formation of red cell resetting‘Cytoadherence’ leads to sequestration of the parasites in various organs such as the heart, lung, brain, liver, kidney, intestines, adipose tissue, subcutaneous tissues, and placenta. If the cytoadherence-resetting-sequestration of infected and uninfected erythrocytes in the vital organs goes on uninhibited, it ultimately blocks blood flow, results in tissue hypoxia. It also hampers mitochondrial ATP synthesis, and stimulates cytokine production which again show severe inflammation, activation of platelets, microcirculatory dysfunction. All these factors are responsible for the development of severe malarial symptoms.

Systemic manifestation in Malaria such as headache, fever and rigors, nausea and vomiting, diarrhoea, anorexia, tiredness, aching joints and muscles, thrombocytopenia, immunosuppression, coagulopathy, and altered functions of central nervous system occur due to Cytokinin release.P. vivax preferentially infects only young RBCs, thus limiting its reproductive capacity and resultant parasite loads and develops symptoms with less magnitude than P. falciparum.[36,37.]

Cytokinin Release syndrome (CRS): - CRSis a systemic inflammatory response that can be triggered by a variety of factors such as infections and certain drugs. The term “cytokine release syndrome” was first coined in the early ‘90s. The term "cytokine" is derived from a combination of two Greek words - "cyto" meaning cell and "kinos" meaning movement. Cytokines are small proteins that help cells around the body communicate. When the immune system detects a threat, cells release cytokines which stimulate the movement of cells towards site of inflammation infection, and trauma.

In CRS, the immune system is overactive. The elevated cytokines cause harmful levels of inflammation throughout the body, which disrupts normal bodyfunctions by acting on immune system. The inflammation may interfere with organ function and cause severe symptoms. CRS can occur due to infection or as a result of certain medical treatments.During an acute malaria infection, cytokines and chemokines are elevated in peripheral blood and contribute to parasite clearance but are also likely to be responsible for many of the symptoms and pathological changes seen during malaria disease.

CRS can present with a variety of symptoms ranging from mild, flu-like symptoms to severe life-threatening manifestations due to severe inflammatory response. Mild CRS shows some constitutional symptoms like fever with rigors malaise, fatigue, anorexia arthralgia, nausea, vomiting, headache, loss of appetite, allergic rashes on skin are seen.More severe cases are characterized by hypotension as well as high fever and can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure.Systemic symptoms regarding cardiovascular system shows tachycardia, arrhythmia, hypotension, in early-stage cardiac output get increased and later due to reduced cardiac function it gets diminished to show Pulmonary oedema.

Respiratory symptoms are common in patients with CRS. Mildrespiratory system shows cough and tachypnoea due to hypoxia. But later,progress to acute respiratory distress syndrome (ARDS.) with dyspnoea, hypoxemia, and bilateral opacities on chest X-ray. ARDS may sometimes require mechanical ventilation. Impaired renal symptoms may progress to Acute renal failure (ARF)characterisedby Azotaemia. Hepatic dysfunction causes elevation of liver enzyme which reflects inhyperbilirubinemia and transaminitis.The severe symptoms of CRS involve impairment of CNS and shows symptoms of altered mental status like, headache, confusion, dementia, hallucination delirium, aphasia, paresis seizures.[38]

CRS grading system: - CRS grading system based on the severity of hypoxemia and target organ failure. There are various grading systems for CRS. The “CTCAE” CRS grading scale **uses patients’ response to fluids, vasopressor, and oxygen, as well as their organ toxicities, However, the heavy reliance of this scale on quantification of oxygen support and fluid volumes, which are difficult to standardize.**Another CRS scale uses a combination of clinical features and serum cytokine and C-reactive protein (CRP) levels as criteria for severe CRS.

“Penn” grading scale is based primarily on clinical parameters and not laboratory values of inflammatory markers. It is widely accepted and applied for both immediate and late onset of cytokinin responses such as Cytokine Storm and CRS.These grading systems are further classifyingthe CRS into grade I, II, III and IV depending on mild moderate,severe and life threatening clinical and laboratory parameters.

Grade I – It include the symptoms which are not life threatening and require symptomatic treatment only. e.g.,fever, nausea, fatigue, headache, myalgia malaise.

Grade II– The symptoms require and respond to moderate intervention. Oxygen requirement <40%. Hypotension responsive to fluids or low dose of one vasopressor. It shows grade IIorgan toxicity e.g. grade II creatinine and grade III LFTs.

Grade III– The symptoms require and respond to aggressive intervention. Oxygen requirement ≥40% or hypotension requiring high dose or multiple vasopressors. It shows grade III organ toxicity including grade IV LFTS and grade IIIcreatinine related to CRS and not attributed to any other condition. Coagulopathies require fresh frozen plasma.

Grade IV– The symptoms require ventilator support and grade IV organ toxicity excluding transaminitis.

Grade V– It shows unresponsiveness to treatment leading to death. [39]

Discussion: -Pathogenesis of vishamjwarashows co resemblance to Cytokinin release syndrome in following ways.

1] **On first day of vishamjwara**, asthi-majja dushti occur, showing the symptoms of sandhyasthi,shira-shoola, shiro-ruka, ati-parshvaruka, vepathu. All these symptoms show the symptoms of grade I CRS where all constitutional symptoms are seen such as headache, myalgia, arthralgia. Vepathu means trembling and may be reflected as typical clinical presentation of Malaria i. e. fever with chills and rigors.Bhrama,vilap and glani are the symptoms of majja dushti which shows CNS involvement due to high grade fever with hypotension. Generally, these symptoms occur in successive stages of grade I.

2] **On second day of vishamjwara**, rakta -mamsa dushti shows daha symptom. It is the manifestation of 'Raktamala'pitta dushti in the skin causing allergic rash with burning sensation to all over the body. Cytokinin release damage the skin epithelium by acting through mast cells and shows inflammatory responses such as rashes with localise oedema and burning sensation.

Pindikodveshtan occur due to muscular involvement showing sever fatigue and myalgia. All these symptoms contribute to grade I - CRS requiring symptomatic treatment.Sa-rakta malamootra pravritti and pain at anal and pubic region reflects rakta, mamsa dushti related to specific organ system.

Bhelacharya mentioned asthi,majja, rakta and mamsa dushti but not as medo-dushti. But medo-dushti can be assessed after asthi-dushti as doshas are attaining "Pratilomagati". This medo-dushti affect its sroto-moola dushti as sa-rakta mootra pravritti. In malaria, cytokinin released by destroyed RBCs again infects other RBCs results in bone marrow depression and severe cytopenia. Thus, deformed destroyed RBCs alter the glomerular filtration further leading to kidney damage where haematuria occurs.These symptoms show similarity to grade II - CRS where organ toxicity start to develop showing increase in values of serum creatinine.

3]**On Third day of vishamjwara**, mild kapha and vayu dushti produce symptoms of pranavaha, annavaha and rasavaha srotodushti where kledak,avlambaka kapha dushti along with prana and udanavayu dushti occur. All these result in manifestation of symptoms such as

gaurav, arochaka, chhardi which are corelated to gastrointestinal symptoms like nausea, vomiting, diarrhoea, that occur in gradeI- CRS.

These symptoms may be seen as the symptoms of metabolic disorders due to impaired Liver Function occur in gradeIII - CRS.When severekapha and vayu dushti occur in pranavaha srotas, it may show arishta lakshanas like hikka, shwasa. These symptoms are corelated to grade III - CRS symptoms where organ toxicity causes increase in serum creatinineand Liver function tests (LFTs). So, Acute kidney failure occur due to uraemia which ultimately results in hiccups. Increased pulmonary infiltration due to CRS related vascular leakage results in sever dyspnoea where oxygen requirement is more than 40%.

Circulatory electrolyte imbalance produces hypotension, sever malaise which reflect as urasada, trishna, kanthashushkata, mukhashosha and nidra viparyaya.

4] **On fourth day of vishamjwara**, severepitta dushti occur means particularly dushti of 'Bhrajak pitta' and 'Raktamala pitta' occur. It manifested as daha, jwara and murccha. 'Pitta' and 'Rakta' are ashraya-ashrayi bhava to each other hence advanced stages of 'Raktamala Pitta'in yakrita reflect as sa-rakta mala-mootra pravritti. Also severely vitiated 'Alochaka pitta' shows drishti-kshaya which reflects blurred vision. All these symptoms can be corelated with grade IVthCRS complications where sever **organ toxicity** excluding**'Transaminities'** develop and need ventricular support.Due to severe organ toxicity, hepatic encephalopathies and acute renal failure symptom occurs which cause murccha. Also sever hepatic damage causes 'coagulopathies' leads to haemorrhagic condition like DIC. which reflect as sa-rakta malamootra pravritti.Severe renal failure causes electrolyte imbalance especially sodium and potassium depletion results in dehydration related acidosis and can be corelated with daha and murccha.Blurred vision may occur in hepatic encephalopathy. Retinopathy due to DIC cause blindness and is corelated with drishti kshaya lakshana.

Conclusion: -Vishamjwara samprapti and its lakshanas as per Bhelacharya showing theoretical correlation with Cytokinin release syndrome which occur in malaria. As successive days of vishamjwara shows dushti of asthi-majja, rakta-mamsa, kapha-vayu and pitta doshas respectively. When these doshas and dushyas are mildly aggravated they show general constitutional symptoms of CRS grade I, and when these dosha – dushyas are vitiatedand aggravated by all its quality and quantity results in 'Sroto-mooladushti' which deepens the samprapti. This sroto-moola dushti manifests as '**organ toxicity'** in terms of CRS.

So, it can be observed that when symptoms are mild on first and second day of vishamjwara are corelated with CRS grade I. Severe symptoms of vishamjwara on first and second day are corelated with CRS grade II symptoms. The third- and fourth-day symptoms of vishamjwara are corelated with grade IIIrdand IVthCRS complications respectively.CRS is a group of syndromes and its grading scale is variable according to its clinical presentation and laboratory investigations. It needs further clinical study to establish standardize CRS grading in terms of Ayurved samprapti lakshanas.But vishamjwara samprapti by Bhelacharya gives clear cut idea about involvement of dosha-dushya on successive daysof vishamjwara. It provides a guideline for the treatment of vishamajwara which ultimately helps to prevent the crisis regarding the CRS.

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