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Thalassemia Major- A Critical Review Through Ayurveda

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Abstract

Thalassemias are a heterogeneous group of inherited disorders characterized by abnormal synthesis of hemoglobin that result from an alteration in the rate of goblin chain production. A decrease in the rate of production of the globins [mainly alpha (α) and beta (β)] impedes hemoglobin synthesis leading to early excessive destruction of red blood cells. This causes hypo chromic, microcytic anemia, one of the characteristic presenting symptoms of thalassemia. The disease thalassemia has not been described as such in Ayurveda but in both thalassemia and Paandu Roga the main cardinal feature appears to be the same i.e., Paandutva. And the genetical basis of this disease is also well established. The terms Kulaja, Anuvamshika or Sahaja are mentioned in our classics to denote the inheritable nature of the disease. Thus, the name given to the disease thalassemia like Kulaja Paandu / Anuvamshika Paandu appears to be appropriate to define this disease entity and nomenclature coined as Beejadushtijanya Pandu. It can be understood that Pitta pradhana Tridosha affects the functions of Raktavaha srotas and ultimately the process of formation of Rakta Dhatu is affected and results in Raktavikriti.

Keywords: Globin Chain, Genetic, Beejadushtijanya Pandu, Thalassemia Major.

Introduction

Thalassemia is a malignant type of genetic disorder affecting millions of people worldwide. Even though many preventive programs are conducted the disease is still remains in higher prevalence level. Hence management of thalassemia may become a very serious problem and it will burden the world's blood bank supplies and the health system in general. So, there is a current need of developing a systematic approach for proper analysis of pathology of this disease and finding out an effective management.

Historical Background

The disease thalassemia was not recognized as a clinical entity until 1925. In 1925 in the United States, the American pediatricians Cooley and Lee described a disease, named Cooley's anaemia in children of Italian and Greek immigrants, today known as Thalassemia Major or Mediterranean anaemia. In India the first case of thalssemia was described by Dr. M Mukherji from Kolkata.[i] The historical developmental events of Thalassemia can be divided into four phases:

Table 01: Developmental events of Thalassemia

PHASE	PERIOD	FACTS
Phase-1	1925-1940	The Thalassemias were classified into major, intermedia and minor types based on their clinical severity (phenotype).
Phase-2	1940-1950	The exact inheritance and genetic basis for the disorder were understood.

Phase-3	1950-1960	The widespread geographical distribution and various types were documented; e.g. α, β, γ etc.
Phase-4	1960-1985	Various molecular defects, prevention by antenatal diagnosis and treatment of Thalassemia Major using the hyper transfusion regimen, iron chelation therapy, BMT etc. evolved

Table 02: β- thalassemia clinical types with genotype.[ii]

Clinical Type	Genotype
1. Thalassemia Major	β^0/β^0, β^+/β^+, β^0/β^+, $\delta\beta^{Lepore}$ / $\delta\beta^{Lepore}$
2. Thalassemia Intermedia	β^0/β, β^+/β^+, (Black)
3. Thalassemia minor	β^0/β, β^+/β

Mutation in Globin Gene Locus

The thalassemia syndromes are caused by mutation at the globin gene loci on chromosome 11 and 16.[iii] The thalassemia syndromes were the first genetic disease to be understood at the molecular level.

Genetic Mutation According To Ayurveda

Even though the origin of Ayurvedic system of medicine was beyond thousands of years ago, Ayurvedic achaaryayas who had vast spectrum of knowledge have described about genetics at the very minute point such as Beeja, Beejabhaaga, Beejabhaagaavayava. And also genetical basis for various diseases like Arsha (hemorrhoids), Prameha (Diabetes), Kushtha (skin disease) etc have been mentioned. Furthermore they have described possible cause of Beejadushti (mutation) in the form of Maatru-Pitru Apachaara, Daiva, Poorvakrita Ashubha Karma and Prakopa of Vaatadi Dosha.

The role of above causative agents in causing mutation till date is a matter of great investigation. Whatever may be the nature and extent of Uptapti[iv] of Beeja Dosha our ancient Aachaaryas concentrated on the resultant variability or the Phenotypes. They also used terms like Upahatatva[v] and Upatapti to describe myriad of clinical consequences due to mutation. Furthermore it has been discussed the possible grave consequences in the form of Tridosha Prakopa, Vikrita Avayava formation corresponding to biochemical abnormalities / functional abnormalities and structural defects.

As far as thalassemia is concerned, there is Upatapti of Beejabhaagaavayava in Beeja which is responsible for the formation of Rakta Dhaatu, which can led to Lakshanas of Tridosha Prakopa. Thalassemia can be correlated to Beejadushtijanya Paandu Roga according to Ayurvedic fundamentals. In Ayurvedic classics, these genetically determined diseases come under Aadibalapravritta Kulaja Vyaadhi[vi] and Sahaja Vyaadhi[vii] and prognosis of these Vyaadhi is said to be Asaadhya in nature[viii].

In Ayurvedic authentic texts, it cannot be found a disease similar to thalassemia. But the methodology of understanding an unknown disease has been described According to aacharya Charaka the key points like Prakopanam, Yonim, Utthaanam, Aatmaanam, Adhishthaanam, Vedanam, Samsthaanam, Shabda, Sparsha, Roopa, Rasa, Gandha, Upadravam, Vriddhi, Sthaana, Kshaya, Udarkam, Naamam, Yogam and Prateekaaraartha Pravritti and Nivritti should be considered to form a concrete base on any disease and to formulate suitable regimen for the disease [ix].

Etiology of Thalassemia Major

It implies the possible Sampraapti of the disease Thalassemia Major. In the red cell precursors due to globin gene mutation there is a decreased hemoglobin synthesis. Ayurveda says that due to the Upahatha Beeja which is responsible for Rakta Dhaatu Nirmaana, there will be Rakta Dhaatwagni Dushti which lead to Vikrita and decreased Rakta Dhaatu Nirmaana.

Involvement of Doshas

As mentioned earlier the possible causes of mutation (Beejopatapti) were discussed like Poorvakrita Karma, Apachaara by both parents etc. But how these causes lead to mutation? This question needs further scientific inquiry. The possible mechanism may be as, due to Anuchita Aahaara – Vihaara of the parents Doshas predominantly Vaata and Pitta vitiated and circulating through the body and at the cellular level mutate the genetic code of cell. It might results in altered functioning of the Dhaatu. It may also result into its destruction or abnormality, and leads to changes in the Prakriti of Dhaatu which results in Dhaatu Vikriti.

Here the involvement of Vaata and Pitta Doshas can be considered because inside the body Vaata Dosha is the initiator of any change, while the transformation or mutation caused by Pitta Dosha. Hence, in this condition Vaata and Pitta Doshas are equally responsible for Prakriti Vaipareetya of Dhaatu. Prakriti of each Dhaatu is maintained by Kapha Dosha. Changes in Prakriti denote Shleshma Kshaya tending to Dhaatu Vaipareetya.

Table 03: Sampraptighataka

Dosha	Tridosha (Mainly Vaata and Pitta)
Dushya	Sarva Dhaatu (Rasa, Rakta mainly), UpaDhaatu & Malas
Agni	Jatharaagnimaandya & Dhaatwagni maandya
Srotas	Sarvasrotas (Rasavaha, Raktavaha mainly)
Srotodushti	Sanga
Udbhavasthaana	Beeja, Aamaashaya
Adhishthaana	Shareera,Mana
Vyaktasthaana	Twak
Rogamaarga	Baahya

Apachaara done by the parents and Poorvakrita Karma might be a contributing factor in the vitiation of Doshas, which might increase the susceptibility to the infection by P. falciparum. Both the parents with Upatapta Shukra (father) and Upatapta Shonita (mother) give rise to Upahata Beeja (zygote), which is homozygous condition for the mutated (Upatapta) globin genes.

The individual which will develop from this zygote will have defective hemopoetic stem cell. In the red cell precursors due to globin gene mutation there will be Rakta Dhaatwagni Dushti at the Beeja level which led to Vikrita and decreased Rakta Dhaatu Nirmaana (decreased hemoglobin synthesis). This severely affects the Poshana and Nirmaana of Uttarottara Dhaatu. Again, there is formation of Malaroopa Rakta Dhaatu which is unable to carry out the physiological functions attributed to it. Paachana of such Malaroopa Rakta Dhaatu leads to formation of Aama. Along with all these factors and Tridosha prakopa result in the Oja Kshaya and ultimately lead to the clinical features of thalassemic patients.

Pathophisiology of thalassemia

Thassemia are Characterized by an imbalance in the production of α and β- globin polypeptide chains of hemoglobin. In α- thalassemia, α chain synthesis is decreased. In β thalassemia β chain synthesis is decreased. Excessive a chain precipitate in red cell membrane and damages it. This leads to premature red cell destruction both in the bone marrow and peripheral circulation particularly in reticuloendothelial system of spleen.

Synthesis of gamma chains persists after fetal life. Increase fetal hemoglobin (HbF) with its high affinity for oxygen leads to tissue hypoxia, which in turn stimulates erythropoietin secretion leading to both medullary and extramedullary erythropoiesis expanses bone marrow space causing a characteristic hemolytic facies with fronto parietal and occipital bossing ,malarprominence and malocclusions of teeth an complication that include distortion of ribs and vertebrae and pathological fracture of the bones, splenomegaly and its complication like hypersplenism, hepatomegaly ,gallstone and chronic leg ulcers.[x]

Possible Samprapti(prognosis) of Upahata Beeja (mutation)

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Table 04: Probable Clinical Features (Roopa) of Thalassemia Vis a Vis Paandu and Halimaka

Thalassemia	Paandu	Halimaka[xi]
Pallor	Twak Paanduratаa	Paanduvarna
Reduction in Hb	Raktaalpataa	-
Chronic fatigue	Gaatrasaada	Utsaahahaani
Weakness	Durbala	Bala Haani
Irregular fever	Jwara (P)	Manda Jwara
Anorexia	Annadwit	Aruchi / Mandaagni
Icteric tinge to sclera	Peeta Netra (P)	Peetavarna
Bronzing of skin	Twak Krishna Paandutva Arunaabhataa (V)	Harita Shyaava Varna
Puffiness of eyes	Akshi Koota Shotha	-
Muscle Cramps	Mruditairiva Gatraaishcha	Angamarda
Hepatomegaly	-	-
Splenomegaly	-	-

Diagnosis of Thalassemia

There are four aspects of the diagnosis viz. carrier screening, antenatal diagnosis, fetal screening and adult screening.

A. Carrier Screening

- Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT)
- Complete Blood cell count:[xii]

B. Antenatal Diagnosis

Fetal blood sampling:[xiii]

C. New Born Hemoglobinopathy Screen.[xiv]

D. Adult Screening

Table 05: Common Laboratory Findings In Thalassemia

CBC	At birth	Adult-hood	Biochemistry
➢ Hb=2-6.5 g% ➢ RBC count: 2-3million ➢ Hct= 10-20% ➢ Red cell Indices: MCV, MCH both decreased ➢ Peripheral smear: ✓ Microcytosis ✓ Hypochromia ✓ Leucocytosis ✓ Reticulocytosis	No HbA	HbF= 70-100 %	➢ TIBC: Decreased ➢ Sr. Ferritin & Sr. Iron: Increased ➢ SGOT, SGPT & Indirect Bilirubin Increased

Treatment

Table 06: Modern Medical Management

1. Transfusion Therapy	4. Stem Cell Transplantation
2. Iron Chelation	5. Gene therapy
3. Splenectomy	6. Other specific managements
4. Bone Marrow Transplantation	

Ayurvedic Management

By following above mentioned treatment principals a proper adjuvant therapeutic plan can be formulated via Ayurveda by selecting drugs from various GANA mentioned in Caraka Samhitaa etc.

Table 07: AYURVEDIC TREATMENT PRINCIPALS

1. Shonita Sthaapana Gana[xv] (Haemostatics)	2. Lohamaarana Gana
3. **Hridya**[xvi] **(Improving Heart Strength)**	4. **Deepaneeya**[xvii]**(Improving Digestion Strength)**

5. Lohashodhana Gana.[xviii]	6. Lohadravaka Gana [xix]
7. **Balya**[xx] **(Improving Strength)**	8. Kakaaraadi Gana

Continuation of Thalassemia Major

In Ayurvedic point of view this disease is be continued due to;

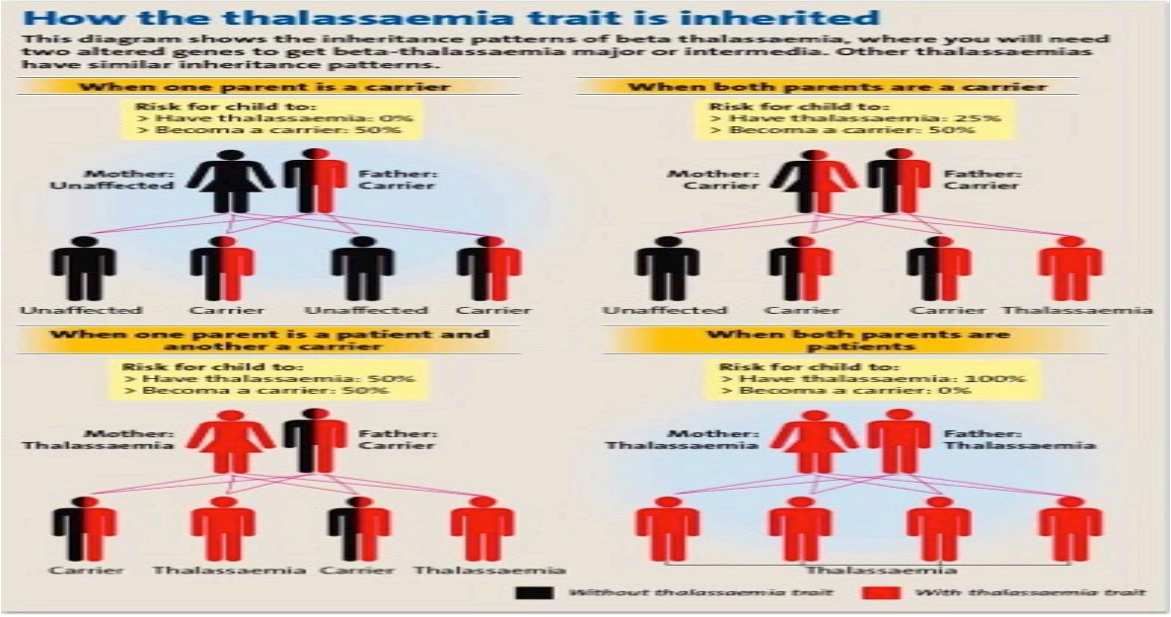
- Nidaana Sevana
- Tulya gotra Vivaaha
- Mithya aahara Vihaara sevana
- Pragnyaparaadha

When considering the current scenario following factors lead to continuation of the disease.

- Consanguinity marriages
- Lack of knowledge
- poverty
- Negligence

Genetic Pattern of Inheritance of B Thalassemia.

The pattern of genetic transmission of beta thalassemia was deciphered by James V. Neel when he was at the University of Rochester (and later at the University of Michigan).[xxi] Thalassemia is an inherited autosomal recessive disorder. When one of the parents is a case of Thalassemia Major then, all the children will be healthy carriers. If a Thalassemia carrier person marries with another Thalassemia carrier, then 50% of the progeny will be born with Thalassemia Major and 50% may be born with ThalassemiaTtrait. When both the parents are carriers of Thalassemia then 25% of the progeny may be born with Thalassemia Major, 50% with Thalassemia Intermedia and 25% of the progeny may be born normal.



Discussion

According to this method, for the nomenclature of the disease thalassemia, the involvement of Dosha and Dushya should be considered. As well thought-out earlier the disease shows the involvement of all the three Doshas along with the

involvement of all the Dhaatus in the form of Kshaya. All the symptoms described in the Sampraapti of Paandu Roga are discernible in the patient of Thalassemia. Thus; thalassemia may be named as Anuvamshika Tridoshaja Paandu. Furthermore ancient Aachaaryas have described possible cause of Beejadushti (mutation).[xxii]Thus also called Beejdustyjanya pandu. Beejdustyjanya pandu and Anuvamshika Tridoshaja Paandu are the severe form of all the types of Paandu with symptoms like Arochaka, Ksheenataa and Hatendriya and the three symptoms are as a rule seen in the Thalassemic patients

Conclusion

Types of pandu described in ayurveda but there is no one to one correlation to Thalassemia with any of these. But In both thalassemia and Paandu the cardinal feature appears to be the same that is Paandutva. Again, the genetical basis of this disease is well established. The terns Kulaja, Anuvamshika or Sahaja are mentioned in our classics to denote the inheritable nature of the disease. In Ayurveda, Aachaarya Charaka described Beejadushtijanya Vikaara. He has explained vitiated doshas may afflict the Beeja or the Beejabhaaga by which the corresponding organs derived from these Beejas and Beejabhaagas get deformed. Ayurvedic concepts and nomenclature was coined as Beejadushtijanya Paandu. Thus, the name given to the disease thalassemia like Kulaja Paandu / Anuvamshika Paandu/Beejdustijanya pandu appears to be appropriate to define this disease entity.

Sourse of Support- Nill

Conflate of Interest- None Declared

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