WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 12, 958-973. Review Article ISSN 2277– 7105

HEREDIATRY HEMOCHROMATOSIS "AN ETIOLOGICAL CONCEPT"

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Article Received on
13 July 2022,

Revised on 03 August 2022,
Accepted on 23 August 2022

DOI: 10.20959/wjpr202212-25438

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ABSTRACT

Hemochromatosis is now considered as an inherited autosomal recessive disorder. In 1935 it was identified as inherited disease. It mainly occur in caucasian with a prevalence of 1 in 300 to 500 individual. In this disorder iron is deposited in many organ and due to this, various complication arises like cirrhosis and fibrosis. HFE gene, which is located on chromosome no. 6 is responsible for the absorption regulation of iron in the body. HFE gene produce a protein called HFE protein that is bound to transferrin and thus regulate the absorption of iron from intestine. Mutation in the HFE gene cause production of altered protein, this can ultimately lead to the disruption in the absorption of iron. Low hepcidin secretion leads to increased duodenal absorption of dietary iron, most commonly in C282Y homozygous individual.

KEYWORDS: Cirrhosis, Ferritin, Hemochromatosis, Hepicidin, HFE Protein.

INTRODUCTION

Hemochromatosis is an autosomal inherited disease. It was first identified in 1800s and then in 1935 it understood to be an inherited disease.[1] Hemochromatosis is the common disorder in united state and it affect people approx 1 million. Northern European people was mainly affected by this disorder. Hemochromatosis happpened due to continuously absorption of iron through small intestine from daily diet. Normal iron absorption rate is 1-2 mg per day, it occur throgh small intestione. In hemochromatosis person this absorption rate reaches upto 4-5 mg per days. So, it causes increase the quantity of iron in the body and too much iron causes toxicity. It accumulated into various organ/tissue and damage the organ this can lead to the development of disease like diabetes mellitus and cirrhosis.[2] Liver is the most affected organ by hemochromatosis because of it's high blood flow. Cirrohis is developed when iron

deposited and accumulated in the liver tissue.[3] Hemochromatosis also called as bronze diabetes because iron damage the pancreatic cell, which is responsible for the production of insulin. Damaged pancreas does not produced insulin properly.[4] Hepcidin protein is responsible for the regulation of iron in the body, development of hemochromatosis is due to the failure of regulation of iron by hepcidin protein found in liver.[5]

Etiology

Hereditary Hemochromatosis is an autosomal recessive genetic disorder that occur in approximately 1 in 300 people, it is mainly associated with the deficiency of iron regulatory hormone called hepcidin. it can damage various types of organ like liver, pancreas, joints, heart, skin and gonad. In herediteryhemochromatosis, deposition of iron in parenchyma cell although transfusional Hemochromatosis deposition of iron in the reticuloendothelial cells. Iron is deposited on different organs of body and can cause organ damage.[6] Mutation in the hemochromatosis gene(HFE) results in occurance of hereditary hemochromatosis. Most common mutation seen in the gene are C282Y and H63D. mutation in the gene leads to increase the absorption of iron content despite a normal dietary iron intake.[7]

Hereditary Hemochromatosis must be distinguished from secondary forms of iron overload, such as those caused by repeated red blood cell transfusion or anaemia owing to ineffective erythropoiesis. The european association for the study of the liver (EASL) define hereditary Hemochromatosis as C282Y homozygosity and increase body iron store in organ without any symptom shown.[8] A report of meta analysis of 2802 european people had seen clinical iron overload found that 81% were homozygous for the C282Y mutation in the HFE gene on the short arm of chromosome 6. A smaller portion of like 5% were compound heterozygous for the C282Y mutation. Other mutation is also seen in the gene but it is rare.[9] Prognostic review found that 75% of homozygous people have raised iron parameter like ferettin and transferrin in blood. The clinical penetrance in men is about 40% and female in about 10%[10], the lower penetrance in female is due to iron loss through menstrual bleeding and childbirth.[11]

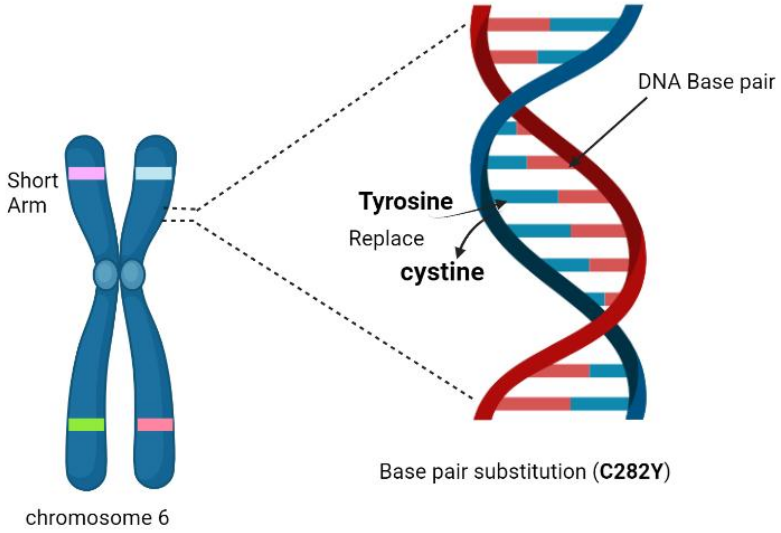


Figure 1. Diagramatic representation shows Base pair substitution mutation (C282Y) in the chromosome no. 6.

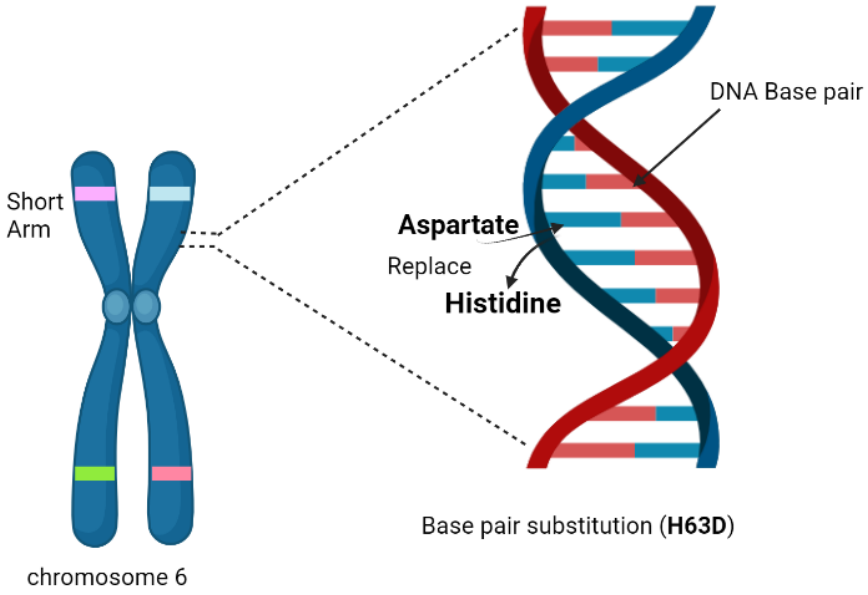


Figure 2. Diagramatic representation shows Base pair substitution mutation (H63D) in the chromosome no. 6.

Balance and Regulation of Iron

Body iron content is regulated by the complex regulation of dietary iron absorption from G.I tract. No any pathway present in the body for the removal of excess iron. Daily involuntary losses of ~1 mg occur via desquamation of cell in G.I tract. Additional iron loss occur in

female due to menstrual loss and pregnancy, so this can result to require to absorb 1-2 mg/days of dietary iron to maintain normal iron balance. Iron is mostly present in haemoglobin with some amount (300mg) in myoglobin. Iron containing enzymes involved in respiration present in all tissue and there is a small amount of iron bound to transferrin (Tf) at any one time in the plasma and extravascular circulation. Transferrin is a glycoprotein, produced in liver and it regulated by body iron stores. In iron deficiency condition production of transferrin is increases and in iron overload condition production of transferrin is decreases. Two iron binding domain is present in each transferrin molecule. In the course of 24hr transferrin will transport 20-40 mg of iron to the tissue from body stores unit. Cell accepts iron from transferrin via interaction with their cell surface transferrin receptor. Iron will accept more readily in diferric state rather than monoferric state.[12] Ferritin is responsible for the safe storage of iron in a readily accessible soluble form. Ferritin is present in all cells. In case of intracellular excessive iron form, ferritin molecule may aggregate to form insoluble haemosiderin. Macrophage of RES is the largest body iron store, which in health may store upto 1g of iron in either ferritin or haemosiderin.[13]

Epidemiology and Prevalence

The major cause of spreading hemochromatosis is lack of awareness, long latency period and non-specific symptoms. Hereditary hemochromatosis is the major common autosomal recessive disorder occur in caucasian with a prevalence of 1 in 300 to 500 individual.[14] Type 2,3 and 4 hereditary hemochromatosis is seen worldwide but type1 form is mostly seen in people of northern european descent.[15] Symptoms of hereditary hemochromatosis in female are seen later than men due to blood loss and consequent iron excertion associated with mensuration.

Prevalence of C282Y homozygosity is approximately one out of 250 in population of predominantely northern european descent.[16-18] Feder et al. in 1996 initially reported the presence of mutation in large proportion of patient.[19] Two types of mutation i.e C282Y and H63D mutation seen in HFE gene in most of Hemochromatosis patient (especially those of north european origin). These mutation are characterized by replacement of cysteine with tyrosine at position 282 and histidine with aspartic acid at position 63.

The mean prevalence of C282Y allele varied is approximately 6%.[20] The frequency varies between 5-10% in other northern european countries.[21-22] It is seen less frequent in ~1-2% in southern Europe[23] and extremely rare in nonwhite population.[24] Approx 90% of individual

with hereditary hemochromatosis are C282Y homozygotes while 5% or less are C282Y/H63D compound heterozygotes.[25-26]

Role of HFE gene In Absorption of Iron

HFE gene make a protein called HFE protein, this protein is associated with transferrin receptor/transferrin complex in the duodenal epithelia. The role of HFE protein in this complex is to modulate the uptake of transferrin bound iron into epithelial cells. HFE protein allow the transferrin complex to act as sensor of body iron stores. mutation in the HFE gene leads to production of Mutated protein, that leads to up-regulated, increased iron absorption. Increased intracellular iron causes peroxidative injury to phospholipid of organelle membrane such as lysosomes, mitochondria and microsomes. Free iron content is the important in the formation of highly reactive hydroxy radical, which ultimately initate lipid peroxidation. Lipid peroxidation induces cell degeneration, cell death, and collagen synthesis that results in fibrosis and cirrhosis.

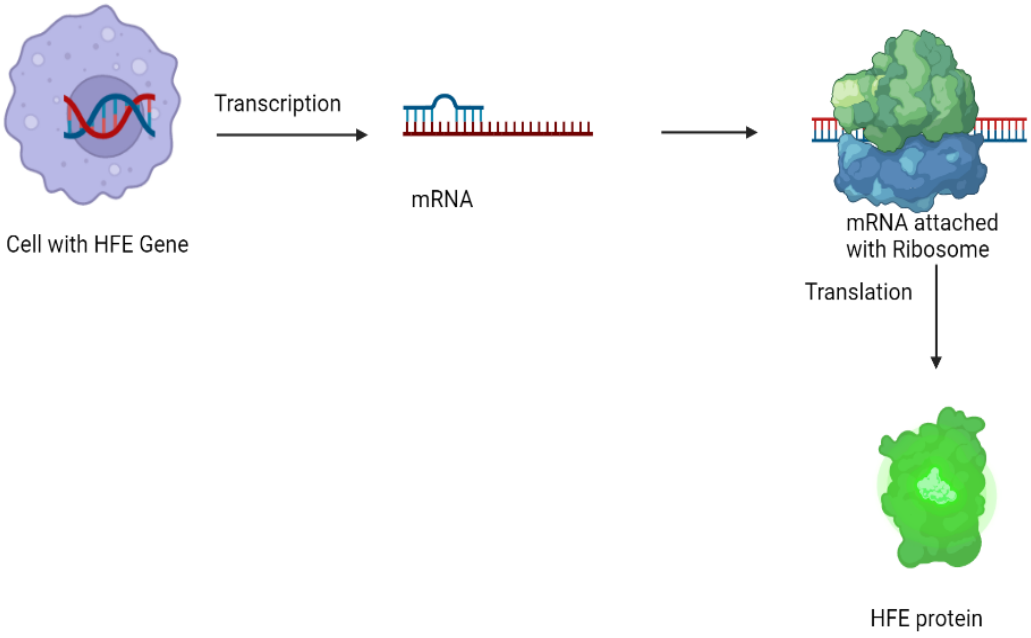


Figure 3. Diagramatic representation shows the production of HFE protein.

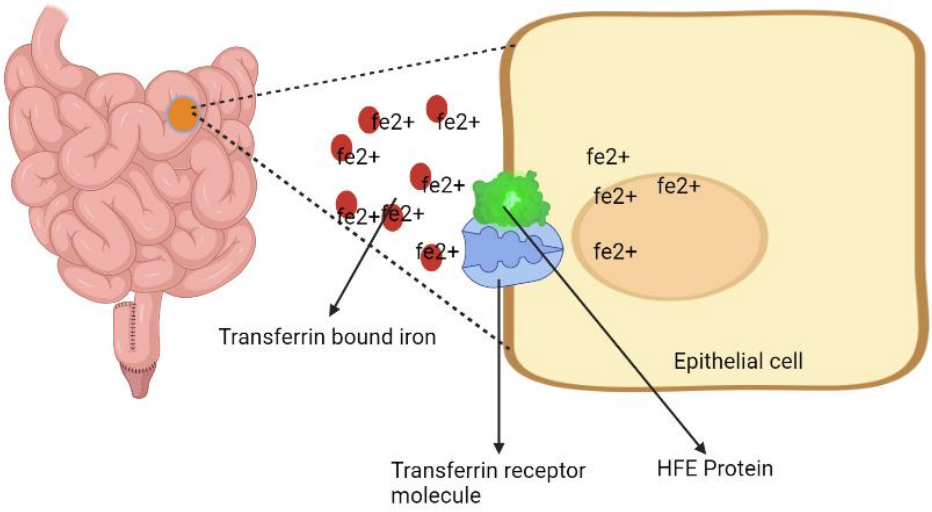


Figure 4. Diagramatic representation shows the transport of transferrin bound iron through the transferrin receptor mediated through HFE protein.

Role of hepcidin in balance of iron

Hepcidin is a protein product produced by hepatocyte. It is a 25 amino acid peptide which is cleaved from prohepcidin and released into the circulation. It control the iron metabolism by binding to ferroportin. Ferroportin is a major cellular iron exporter.[27] Ferroportin is degraded by via lysosomal pathway, thus it leads to reducing iron efflux from cell.[28] Reduction in no. of hepcidin mediated ferroportin in the enterocyte leads to decrease in intestinal absorption of iron and this consequently reduced body iron stores.[29] Human body does not have any other mechanism for removing the excess iron, so hepicidin mediated reduction of iron absorption is the major way by which body regulate iron stores. So, in case of iron deficiency, hepcidin expression is reduced leading to increase iron absorption.[30] In reverse condition like excess of iron, excessive concentration of iron is sensed by hepatocyte via increased serum TS, production of hepcidin is increased leading to iron with holding within cells, thus ultimately reducing iron efflux from iron storage site and intestinal iron absorption.[31]

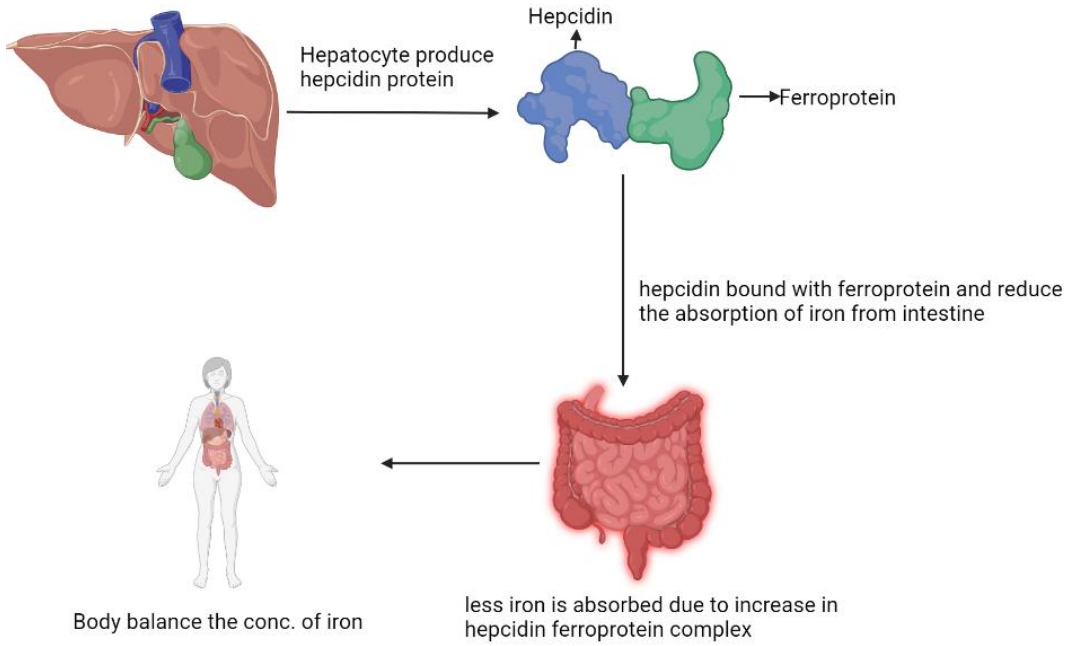
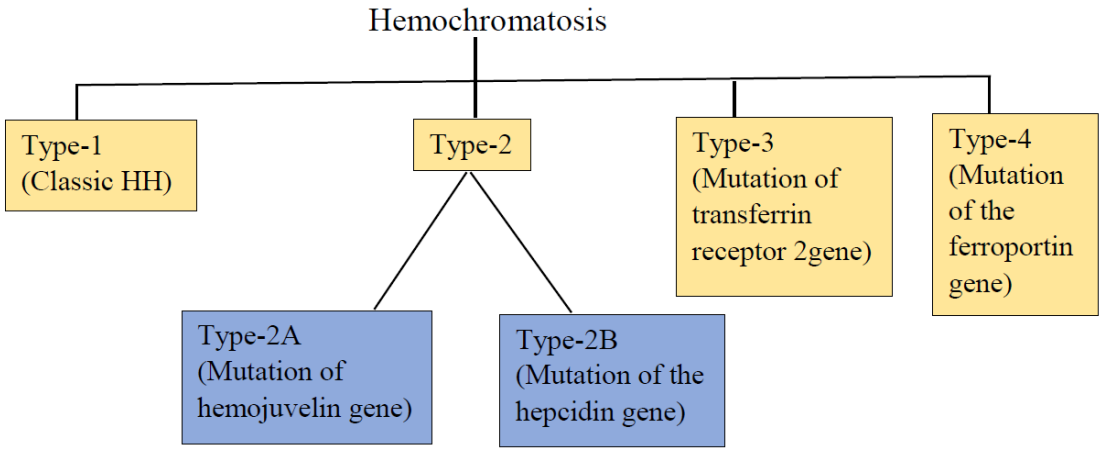


Figure 5. Diagramatic representation shows the body balance the iron concentration through hepcidin mediated ferroprotein.

Types of Hemochromatosis



Clinical Outcomes

Hemochromatosis is related to the accumulation of iron in different body parts like liver, pancreas, heart, pitutary, skin and joints. The accumulation of iron on these organ leads to the development of other complication like fibrosis, cirrohsis, hepatocellular carcinoma, diabetes, cardiomyopathy, impotence, hypogonadotrophic hypogonadism, abnormal increased skin pigmentation and arthritis involving the second and third metacarpophalangeal joints.[32-33]

- Cirrhosis is present in about 75% of patient with hemochromatosis, it occur due to the accumulation of iron in the liver. it leads to the major cause of death.

- Diabetes is developed because of iron deposition on the beta cell of pancreas that cam ultimately damaged the insulin producing beta cell. The incidence of diabetes is approximately 50% in symptomatic patient.
- Dilated cardiomyopathy and cardiac arrhytmias are the clinical manifestation related with cardiac system arised due to accumulation of iron in the cardiac muscle fibers and cells of the conduction system.
- Arthropathy related with the joint pain without joint destruction. Calcium pyrophosphate crystal can be found in the synovial fluid, it can still progress after normalization of iron stores.
- Deposition of iron in the thyroid gland causes hypothyroidism. The chances of hypothyroidism is 80 times greater than normal for men with hemochromatosis.

There are 3 ways by which iron overload that cause hemochromatosis:-

1. Massive oral intake of iron
2. Increased iron absorption with normal iron intake
3. Excessive production or massive transfusion of red blood cells.

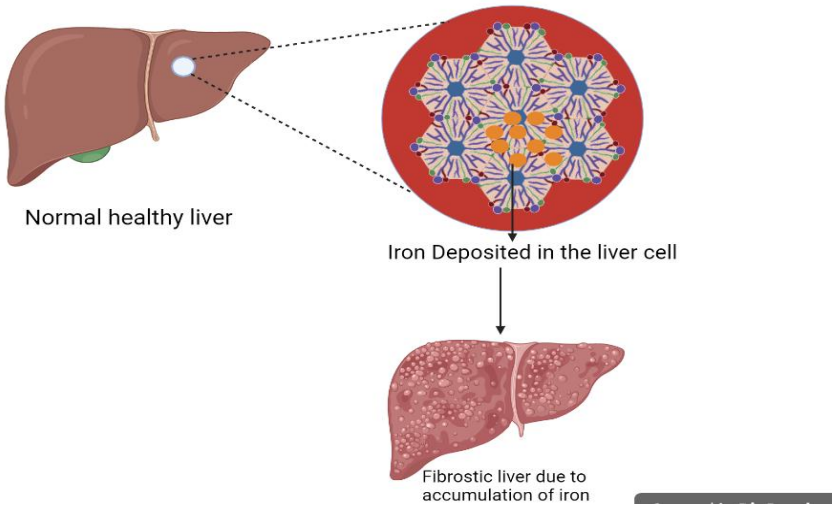


Figure 6. Demonstrate the iron deposition in the liver cell cause fibrosis.

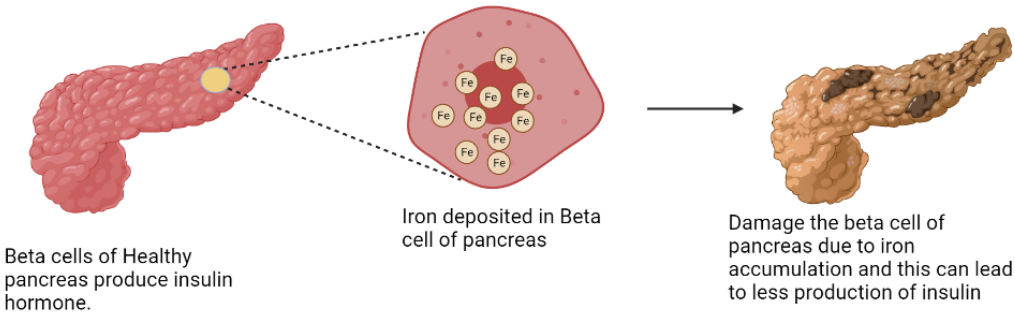


Figure 7. Demonstrate the iron deposition in the pancreas cell cause beta cell necrosis.

Diagnosis

Hemochromatosis is diagnosed through patient history, physical examination, blood test and liver biopsy. Patient who have shown the symptom of hemochromatosis should be evaluated for screening and diagnosis. High serum iron demonstration, transferrin saturation(greater than 60% in men and post menopausal women or 50% in premenopausal women) demonstration and elevated serum ferritin value (>300υg/L in male and >200υg/L in premenopausal female) suggest hereditary hemochromatosis.[34] A liver biopsy is recommended in patient with elevation of both serum transferrin saturation and serum ferritin to evaluate the extent of iron overload and hepatic damage.[35] HFE testing is needed only in those condition where the patient transferrin saturation level is increased. These increased saturation of transferrin is diagnosed by excluding the cause of hyperferritinaemia like inflammation, alcohol consumption, liver cell necrosis, metabolic syndrome(blood pressure, body mass index, triglyceride, and glucose).[36] People who have symptom of Hemochromatosis and who are C282Y homozygous typically have higher than normal transferrin saturation and ferritin, as a result of disrupted iron homeostasis. So, in this case diagnosis of HFE can be established.

Transferrin Saturation

It is the proportion of iron transport protein that is saturated with iron. It is calculated as:- serum iron(υmol/L):25/ transferrin(g/L)*100%. In hemochromatosis condition, the level of transferrin is generally increased throughout the day. Transferrin saturation level increases results in innately low hepcidin level which leads to increased iron uptake from intestine and iron release by reticuloendothelial macrophage.[37] People who have iron loading anaemias and who take iron tablet or multivitamin that contain iron has also increased level of transferrin saturation.

Serum ferritin

Serum ferritin is an indication of body iron store and is increased in patient with iron overload, viral infection, other inflammatory condition, the metabolic syndrome, cancer, and chronic liver disease. Serum ferritin level can be measured by various immuno-chemical methods.

Genetic testing

When patient show similar symptoms and iron overload then genetic testing is needed for the confirmation of hemochromatosis. A systematic review found sensitivity and specificity of C282Y homozygosity to be almost 100% respectively for the presence of an iron overload phenotype in white northern Europeans.[38] If patient are C282Y homozygotes then screening of first degree relatives for the presence of the genotype may be indicated.[39]

MRI and Liver biopsy

Magnetic resonance imaging is a helpful technique in diagnosis of hemochromatosis. It is used when diagnosis is still unsure after blood analysis and testing for the C282Y and H63D polymorphism of HFE gene. MRI is a very reliable technique for the detection of iron in the liver.[40] In liver biopsy the cell of iron deposited liver is withdrawn and it can be analysed to look iron deposit. If the conc. Of iron deposition is below the cutoff value, the hemochromatosis can be excluded.[41]

Prognosis of patient with hemochromatosis

The risk of development of liver disease and hepatocellular carcinoma is more in patient with C282Y homozygous hemochromatosis.[42] A population screening survey of 65278 people shown that the absolute risk of liver damag is about 5% in homozygous men and less than 1% in women.[43] These complication reduces the life expectancy of patient. However patient who take proper treatment and routinely follow chekup shows low mortality rate than general population.[44-45]

Prevention approach

Population screening:

Population screening is recommended by several authors due to the relatively high prevalence of C282Y homozygous genotype in european population.[46] Due to the incorrect diagnosis of hemochromatosis, many of the people found low clinical penetrance which not clinically

unwell which could be harmful and could lead to problem with obtaining medical insurance.[47]

Screening of people with positive family history:

Relatives screening of patient family is the another best option for the prevention of disease hemochromatosis. A study shows that a patient with two children, the more cost effective approach is to test the patient spouse first and test the children only if the spouse is heterozygous.[48] Due to unkown risk of development of of symptom and clinical sign of hemochromatosis in homozygous, the value of test for C282Y mutation is still unknown.

Management Approach

Phlebotomy

Phlebotomy is now considered as the best approach in the management of primary hemochromatosis. In phlebotomy, red blood cell is drawn off, which is a major transporter of iron in the body. So, this approach can minimize iron toxicity. It is performed only once /twice in a week. The main objective is to maintain ferritin level less than 50 mcg/L.[49] Each 500ml of blood contain 0.25g of iron. The concentration of iron upon which phlebotomy is indicated is not clear. A meta analysis report shows that serum ferritin conc. Above 1000υg/L cause cirrhosis.[50] Phlebotomy treatment start when serrum ferritin level rises above local reference value (about 300υg/L and 200υg/L for men and women).[51] It is not clear that how much quantity of blood drawn but expert consensus suggest that 500ml blood should be taken each week in depletion state.[52] If the patient have anaemia or any other complication, the frequency of blood withdrawn should be adjusted accordingly patient conditions.

Iron chelation

Iron chelation is the alternative way to phlebotomy. It is more costly and it has several many side effects. It is done with desferrioxamine in which ferric iron bound to ferrioxamine complex and eleminated form body via urine. Side effects includes gastrointestinal symptoms, dizzines, visual and auditory impairment, muscle cramps, tachycardia are observed. Iron chelation is used when phlebotomy is contraindicated.

Therapeutic erythrocytapheresis

Therapeutic erythrocytapheresis is just like phlebotomy in which removal of erythrocytes instead of whole blood.[53]

CONCLUSION

Hemochromatosis is an inherited autosomal recessive iron disorder. It is associated with deposition of iron on different tissues of organ like liver, pancrease, kidney, heart etc. it occur due to mutation cause in HFE that is responsible for the absorption and storage of iron in the human body from intestine. HFE gene are present on the chromosome no. 6. Mutation is mainly associated with the replacement of cysteine with tyrosine at position 282(C282Y) and histidine with aspartic acid at position 63. It can be managed by treatment like phlebotomy, iron chelation and therapeutic erythrocytapheresis. Newly emerging technique is also helpful in the treatment of this disorder.

REFERENCES

1. Yun S, Vincelette ND. Update on iron metabolism and molecular perspective of common genetic and acquired disorder, hemochromatosis. Crit. Rev. Oncol. Hematol, 2015 Jul; 95(1): 12-25.
2. Dooley, J. & Worwood, M. (2000) Guidelines on Diagnosis and Therapy: Genetic Hemochromatosis. British Committee for Standards in Haematology. Darwin Medical Communications Ltd., Abingdon, Oxford.
3. European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. J Hepatol, 2010; 53: 3-22.
4. Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R, Ellis MC, Fullan A, Hinton LM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier GA, Moeller N, Moore T, Morikang E, Prass CE, Quintana L, Starnes SM, Schatzman RC, Brunke KJ, Drayna DT, Risch NJ, Bacon BR, Wolff RK. A novel MHC class I-like gene is mutated in patients with hereditary Hemochromatosis. Nat. Genet, 1996 Aug; 13(4): 399-408.
5. Bridle KR, Frazer DM, Wilkins SJ et al. Disrupted hepcidin regulation in HFEassociated Hemochromatosis and the liver as a regulator of body iron homeostasis. Lancet, 2003; 361(9358): 669–673.
6. Bridle KR, Frazer DM, Wilkins SJ et al. Disrupted hepcidin regulation in HFEassociated Hemochromatosis and the liver as a regulator of body iron homeostasis. Lancet, 2003; 361(9358): 669–673.
7. Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R, Ellis MC, Fullan A, Hinton LM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier GA, Moeller N,

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8. Cuijpers M, Raymakers R, MacKenzie A, de Witte T, Swinkels D. Recent advances in the understanding of iron overload in sideroblastic myelodysplastic syndrome. Br J Haematol, 2010; 149: 322-3.
9. Wood MJ, Powell LW, Ramm GA. Environmental and genetic modifiers of the progression to fibrosis and cirrhosis in hemochromatosis. Blood, 2008; 111: 4456-62.
10. Yen, A. W., Fancher, T. L., & Bowlus, C. L. (2006). Revisiting hereditary hemochromatosis: Current concepts and progress. The American Journal of Medicine, 119(5): 391–399.
11. Wood MJ, Powell LW, Ramm GA. Environmental and genetic modifiers of the progression to fibrosis and cirrhosis in hemochromatosis. Blood, 2008; 111: 4456-62.
12. Young, S., Bomford, A. & William, R. (1984) Effect of iron saturation of transferrin on its binding and uptake by rabbit reticulocytes. Biochemical Journal, 219: 505.
13. Worwood, M. (1982) Ferritin in human tissues and serum. Clinics in Haematology, 11: 275–307.
14. Adams PC. Epidemiology and diagnostic testing for hemochromatosis and iron overload. Int J Lab Hematol, 2015 May; 37 Suppl 1: 25-30.
15. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. N. Engl. J. Med., 1999 Sep 02; 341(10): 718-24.
16. Beutler E, Felitti VJ, Koziol JA et al. Penetrance of 845G → A (C282Y) HFE hereditary Hemochromatosis mutation in the USA. Lancet, 2002; 359(9302): 211–218.
17. Beutler E, Gelbart T, West C et al. Mutation analysis in hereditary hemochromatosis. Blood cells Mol. Dis., 1996; 22(2): 187–194.
18. Bacon BR, Olynyk JK, Brunt EM, Britton RS, Wolff RK. HFE genotype in patients with hemochromatosis and other liver diseases. Ann. Intern. Med., 1999; 130(12): 953–962.
19. Feder JN, Gnirke A, Thomas W et al. A novel MHC class I-like gene is mutated in patients with hereditary Hemochromatosis. Nat. Genet., 1996; 13(4): 399–408.
20. EASL. Clinical practice guidelines on hemochromatosis. J. Hepatol, 2010; 53: 3–22.
21. Ryan E, O'Keane C, Crowe J. Hemochromatosis in Ireland and HFE. Blood Cells Mol. Dis., 1998; 24(4): 428–432.

22. Merryweather-Clarke AT, Pointon JJ, Jouanolle AM, Rochette J, Robson KJ. Geography of HFE C282Y and H63D mutations. Genet. Test., 2000; 4(2): 183–198.
23. Sanchez M, Bruguera M, Bosch J, Rodes J, Ballesta F, Oliva R. Prevalence of CYS282 tyr and his63Asp HFE gene mutations in Spanish patients with hereditary hemochromatosis and in controls. J. Hepatol, 1998; 29(5): 725–728.
24. Adams PC, Reboussin DM, Barton JC et al.; Hemochromatosis and iron-overload screening in a racially diverse population. N. Engl. J. Med., 2005; 352(17): 1769–1778.
25. Gochee PA, Powell LW, Cullen DJ, Du Sart D, Rossi E, Olynk JK. A populationbased study of the biochemical and clinical expression of the H63D hemochromatosis mutation. Gastroenterology, 2002; 122(4): 646–651.
26. Olynk JK, Digby JC, Aquilia S, Rossi E, Summerwille L, Powell LW. A populationbased study of the clinical expression of the hemochromatosis gene. N. Engl. J. Med., 1999; 341(10): 718–724.
27. Nemeth E, Tuttle MS, Powelson J et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science, 2004; 306(5704): 2090–2093.
28. De Dominico I, Ward DM, Langelier C et al. The molecular mechanism of hepcidin-mediated ferroportin down regulation. Mol. Biol. Cell, 2007; 18(7): 2569–2578.
29. Steinberg KK, Cogswell ME, Chang JC et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. JAMA, 2001; 285(17): 2216–2222.
30. Nicolas G, Bennoun M, Porteu A et al. Severe iron deficiency anemia in transgenic mice expressing liver hepcidin. Proc. Natl Acad. Sci., 2002; 99(7): 4596–4601.
31. Gan EK, Powell LE, Olynk JK. Natural history and management of HFEhemochromatosis. Semin. Liver Dis., 2011; 31(3): 293–301.
32. Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: a changing scene. Am. J. Med., 1991; 90(4): 445–449.
33. Bacon BR, Sadiq SA. Hereditary hemochromatosis: presentation and diagnosis in the 1990s. Am. J. Gastroenterol, 1997; 92(5): 784–789.
34. Adams, P. C. (2015). Epidemiology and diagnostic testing for hemochromatosis and iron overload. International Journal of Laboratory Hematology, 37: 25–30.
35. Adams, P. C., McLaren, C. E., Speechley, M., McLaren, G. D., Barton, J. C., & Eckfeldt, J. H. (2013). HFE mutations in Caucasian participants of the Hemochromatosis and Iron Overload Screening study with serum ferritin level<1000υg/L. canadian journal of Gastroenterology, 27(7): 390–392.

36. Fischer R, HarmatzPR. Non-invasive assessmentoftissue iron overload. Hematology, 2009: 215-21.
37. Kemna EH, TjalsmaH, WillemsHL, SwinkelsDW. Hepcidin:from discovery to differentialdiagnosis. Haematologica, 2008; 93: 90-7.
38. BryantJ, Cooper K, PicotJ, CleggA, RoderickP, RosenbergW, et al. A systematic review of the clinical validity and clinical utility of DNA testing for hereditary Hemochromatosis type 1 in at-riskpopulations. J Med Gen, 2008; 45: 513-8.
39. El-SeragHB, Inadomi JM, KowdleyKV. Screening for hereditary hemochromatosis in siblings and children of affected patients. Acosteffectiveness analysis. Ann Int Med, 2000; 132: 261-9.
40. SwinkelsDW, Janssen MC, Bergmans J, Marx JJ. Hereditary hemochromatosis: genetic complexity and new diagnostic approaches. Clin Chem, 2006; 52: 950-68.
41. Swinkels D, Jorna A, Raymakers R. Synopsis of the Dutch multidisciplinary guideline for the diagnosis and treatment of hereditary Hemochromatosis. Neth J Med, 2007; 65: 452-5.
42. Ellervik C, Birgens H, Tybjærg-Hansen A, Nordestgaard BG. Hemochromatosis genotypes and risk of 31 disease endpoints: metaanalyses including 66000 cases and 226000 controls. Hepatology, 2007; 46: 1071-80.
43. AsbergA, Hveem K, Thorstensen K, Ellekjter E, Kannelønning K, Fjøsne U, et al. Screening for hemochromatosis—high prevalence andlow morbidity in an unselectedpopulation of 65238 persons. Scand J Gastroenterol, 2001; 36: 1108-15.
44. Niederau C, Fischer R, SonnenbergA, StremmelW, TrampischHJ, StrohmeyerG, et al. Survival and causes of death in cirrhotic and in noncirrhotic patients with primaryhemochromatosis.N Engl J Med, 1985; 313: 1256-62.
45. Jacobs E, Hendriks J, Marx J, vanDeursen C, KreeftenbergH, deVries R, et al. Morbidity andmortality in first-degree relatives of C282Y homozygousprobands with clinically detected Hemochromatosis compared with the generalpopulation: the HEmochromatosis FAmily Study (HEFAS). Neth J Med, 2007; 65: 425-33.
46. EllervikC, Mandrup-PoulsenT, NordestgaardBG, Larsen EL, Appleyard M, Frandsen M, et al. Prevalence ofhereditary Hemochromatosis in late-onsettype 1 diabetesmellitus: a retrospective study. Lancet, 2001; 358: 1405-9.
47. Niederau C, Fischer R, PürschelA, StremmelW, HäussingerD, StrohmeyerG. Long-term survivalin patients with hereditary hemochromatosis. Gastroenterology, 1996; 110: 1107-19.

48. El-SeragHB, Inadomi JM, KowdleyKV. Screening for hereditary hemochromatosis in siblings and children of affected patients. Acosteffectiveness analysis. Ann Int Med, 2000; 132: 261-9.
49. Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. Int. J. Infect. Dis., 2007 Nov; 11(6): 482-7.
50. Ellervik C, Birgens H, Tybjærg-Hansen A, Nordestgaard BG. Hemochromatosis genotypes and risk of 31 disease endpoints: metaanalyses including 66000 cases and 226000 controls. Hepatology, 2007; 46: 1071-80.
51. European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. J Hepatol, 2010; 53: 3-22.
52. European Association for the Study of the Liver. EASL international consensus conference on Hemochromatosis. J Hepatol, 2000; 33: 485-504.
53. Rombout-Sestrienkova E, vanNoordPA, vanDeursen CT, SybesmaBJ, Nillesen-MeertensAE, KoekGH, et al. Therapeutic erythrocytapheresis versusphlebotomy in the initialtreatmentofhereditary hemochromatosis—a pilot study. Transfus Apher Sci., 2007; 36: 261-7.