Review Article

Review of the current literature on H syndrome treatment

Kimia Saleh Anaraki[1], Sepehr Khosravi[2,3], Elham Behrangi[4,5], Afsaneh Sadeghzadeh-Bazargan[4,5], Azadeh Goodarzi[4,5]

[1]General Medicine, Shahid Beheshti University of Medical Sciences, [2]General Medicine, Student Research Center, School of Medicine, Iran University of Medical Sciences (IUMS), [3]Universal Scientific Education and Research Network (USERN), [4]Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), School of Medicine, Iran University of Medical Sciences, [5]Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract

H syndrome is a systemic inherited autosomal recessive histiocytosis, with characteristic cutaneous findings accompanying systemic manifestations and a most common genetic mutation (OMIM 612391) as SLC29A3. The term "H Syndrome" is representative of presentation with hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, low height, and, occasionally, hyperglycemia. H syndrome is new and growing entity in medicine. This syndrome is not specific to a region or a nationality. There are very few treatment experiences on H Syndrome patients and most of them are unsatisfactory apart from hypertrichosis, which is able to treat almost permanently by hair removal lasers. Latest findings suggest that there is possibility of prevention of short stature or other cutaneous or systemic complications in this syndrome with earlier diagnosis and treatment. We searched Medline, Scopus, Web of Sciences, and Google Scholar, up to now and reviewed previous published papers with emphasis on treatment methods and its effects on certain common symptoms.

Keywords: Clinical presentations, cutaneous presentations, H syndrome, systemic presentations,treatment ,therapy

Introduction

H syndrome is a systemic autosomal recessive inherited histiocytosis, with characteristic cutaneous findings accompanying systemic manifestations without any standard treatment for better controlling or progression prevention of the disease.[1,2] The first described cases were form Arab descendant; cases in India and United States were also reported. At now, reports available indicate there are less than 100 patients diagnosed with H syndrome.[3] The term "H Syndrome" originates from the fact that patients in the first study about this syndrome were presented with hyperpigmentation and hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, low height, and, occasionally, hyperglycemia.[4] In all 10 patients of the first cases reported progressive sclerodermatous thickening accompanied by hyperpigmentation of lower and middle body parts were the significant finding.[4] The lesions start to appear mainly in the first or second decade of life.[4] The common sites of hyperpigmentation and hypertrichosis in the largest study on this syndrome determined to be thighs (61%), shins (41%), and genitalia (30%).[5] The pattern of lesion spreading is more likely to be started with thighs, then move upward toward the buttocks and trunk, and this pattern could be helpful for diagnosis.[6] The symptoms based on the mentioned study could be divided into two groups. First, the ones that were more common in the

Address for correspondence: Dr. Azadeh Goodarzi, Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), School of Medicine, Iran University of Medical Sciences, Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: goodarzi.a@iums.ac.ir, azadeh_goodarzi1984@yahoo.com

Received: 17-07-2021 **Revised:** 22-10-2021
Accepted: 13-12-2021 **Published:** 10-03-2022

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1435_21

How to cite this article: Saleh Anaraki K, Khosravi S, Behrangi E, Sadeghzadeh-Bazargan A, Goodarzi A. Review of the current literature on H syndrome treatment. J Family Med Prim Care 2022;11:857-60.

reported patients such as Cutaneous hyperpigmentation (68%), flexion contractures of fingers (56%), hearing loss (53), short stature (49%), hepatomegaly and splenomegaly (43 and 39%), cardiac anomalies (34%), and hallux valgus (30%). Second, the ones that are less common such as exophthalmos and proptosis, arthritis, varicose veins, dilated scleral vessels, facial telangiectasia, and lymphadenopathy.[5] The definite diagnosis is based on genetic consult and mutation analysis.[1,7] H syndrome is new and growing entity in medicine. This syndrome is not specific to a region or a nationality. There are very few treatment experiences on H Syndrome patients and most of them are unsatisfactory despite hypertrichosis. Latest findings suggest that there is possibility of prevention of short stature or other cutaneous or systemic complications in this syndrome with earlier diagnosis and treatment. So we comprehensively reviewed the literatures up to now and emphasized on treatment methods and its effects on certain common symptoms.

Discussion

This worldwide rare syndrome is more recognized and diagnosed in recent previous years. The latest findings suggest that there is possibility of prevention of short stature or other cutaneous and systemic complications in this syndrome with earlier diagnosis and treatment. Cases usually were treated with false dermatologic and rheumatologic diagnosis (especially morphea, sclerodermia, and arthritis) years before the final diagnosis. Given the fact these patients have visited multiple specialties before a final diagnosis it could be concluded that pediatricians, cardiologists, otolaryngologists, dermatologists, internists, and rheumatoligsts might visit these patients. Patients presented with systemic symptoms especially hearing loss, cardiac and orthopedic abnormalities, organomegaly also indurated hyperpigmentated areas in thighs, genitalia, or other areas of body should always be suspected for H syndrome in particular in the setting of hypertrichosis. Sensorineural hearing loss, low growth velocity, cardiac anomalities are common findings in the patients in their first decade of life. Hypogondism in these patients may result in amenorrhea and delayed puberty. The first presentation of this syndrome is in the first or second decade of patients' life (many presentations like cardiac abnormalities may be asymptomatic and an accidental finding), so early diagnosis could help us to find the best regimen for preventive and therapeutic approaches in these patients. No documented treatment was described for this syndrome although hypertrichosis almost permanently response to laser.[8,9] Antinuclear antibody positive was reported in patients, and it is one of pitfalls for misdiagnosing as a rheumatologic entity.[8,10] Short stature as mentioned before is common in H syndrome patients and low-growth hormone, and low IGF-1 levels are also reported in these patients.[4] IGF-1 is also low in juvenile idiopathic arthritis and another pitfall for misdiagnosing. Tocilizumab has been reported to increase growth velocity and IGF-1 levels in H syndrome.[8,11]

There and very few treatment experiences on H syndrome patients. Considering unknown pathophysiology of H syndrome, various unsuccessful treatments have been used. Corticosteroid has partial success on treatment of these patients,[12] while other treatments on these patients include nonsteroidal anti-inflammatory drugs,[13] cyclosporine,[12] methotrexate,[14] cyclophosphamide,[12,15] 6-mercaptopourine,[16] and adalimumab,[5] which are usually associated with no or partial therapeutic success. Also, it is worth mentioning that since this syndrome is a new diagnosis and previously described in the literature with different terms such as nonautoimmune insulin-dependent diabetes mellitus (PHID) syndrome[17] or Rosai–Dorfman disease[18] some symptoms like hearing loss and short stature are missed as part of this syndrome and has been treated as isolated conditions. Bear this in mind, there are far less data on the effects of medication used to treat H syndrome on these conditions.

In a study with five patients, multiple medications such as prednisolone, methotrexate, cyclosporine, and tocilizumab were used to treat the patients. In two cases, patients were on low-dose predinisolone for multiple years since with the discontinuation, and tapering of corticosteroid was accompanied by rise of the subsided symptoms. In these cases, 0.2 and 0.35 mg/kg/day prednisone were continued for several years. The symptom which was resistant to treatment was arthritis. The injection of corticosteroid to joints was used only for short-term solution in these patients and never had long-term impact. Methotrexate resides the symptoms in two cases, but then again, the stiff joints was still the concern of the patient and did not improve with the mentioned treatment. Tocilizumab was the final choice to either add to methotrexate or prednisolone or as a single medication therapy. In cases mentioned in the study, the answer to tocilizumab was noteworthy. Cyclosporine as the medication implemented in our case was tried in the patients of the mentioned study but because it has not affected their arthritis and elevated CRP and had little effects on their lab results was discontinued and other medication was replaced. In one patient in the mentioned study, cyclosporine (3 mg/kg/day) plus prednisolone (0.2 mg/kg/day) was the treatment for 1 year and then the cyclosporine was discontinued, patients symptoms were subsided, and the ESR level was back to normal but then elevated to 50 mm/h.[10] In pathophysiology of H syndrome, IL-6 is reported to have impacts so medications such as tocilizumab could be the future of treatment for H syndrome patients. The impact of tocilizumab on growth velocity for H syndrome patient is reported in two cases, while there is no evidence regarding its impact on hearing loss.[10] Agents that are anti IL-1 or TNF alpha such as adalimumab have been reported to be ineffective in multiple studies.[5,10,19] Treatment with systemic corticosteroid is effective for a while and after tapering the corticosteroid patient symptoms returns. Studies also report that joint stiffness is not affected by corticosteroids.[20]

Current literature indicates success in treatment of many of the H syndrome symptoms with Cyclosporine. What it seems to the advantage of tocilizumab is the fact that this medication has higher success in the treatment of arthritis and could

Table 1: Treatment modalities in some clinical presentations in H syndrome

	Cutaneous Hyperpigmentation	Joint Stiffness	Hearing Loss	Short Stature	Arthritis
Systemic Corticosteroids	Senniappan S, *et al.*[13] Systemic corticosteroid has not been effective in disappearance of lesions in long term			Senniappan S, *et al.*[13] starting corticosteroid has not prevented low-growth velocity of the patient	Bloom JL, *et al.*[10] study systemic corticosteroid did not improve arthritis patient
Cyclosporine	In both, de Jesus J, *et al.* study and Bloom JL, *et al.* study, cylosporine was effective on skin lesions[10,12]	De Jesus J, *et al.*[12] study improved patients joint stifness. While in Bloom JL, *et al.*[10] study cyclosporine has not positive effect on the patient's complaint of joint stiffness		Bloom JL, *et al.*[10] study cyclosporine has not preventive in the case that has been under this regimen	
Tocilizumab				Bloom JL, *et al.*[10] study shows positive effects of tocilizumab on patients' height. This the only case that a medication affects patients final height	Bloom JL, *et al.*[10] study presented a case with improvement in arthritis under Tocilizumab
Mycophenolate Mofetil (the authors of this review reported the first case of H syndrome treated with MM)	In this reported case, Mycophenolate Mofetil improved patients' lesion. Previous lesions start to disappear and there were no sign of new lesions or any adverse effects[21]	Mycophenolate Mofetil also has positive effects on patients' joint stiffness and improved her quality of life and range of motion[21]			Mycophenolate Mofetil in this reported case had also improved clinical and preclinical features of arthritis[21]
Methotrexate	Bloom JL, *et al.*[10] study shows improvement of lesion in one case under this regimen	Bloom JL, *et al.*[10] study shows no effects on joint stiffness under methotrexate			

be potentially successful in the treatment of short stature. One pitfall find in the tocilizumab regimen was in a case that patient had normal CRP levels but clinical symptoms had not improved (the mutation in that patient was SLC29A3) 2.[19] Barring the fact that diagnoses of patients are rarely made in the golden time for their growth cyclosporine based on reports is an impactful regimen for H syndrome patients specifically in the absence of arthritis.

In multiple cases, regimens with multiple medications have better outcomes but the combination of medication differs from patients to patients. Methotrexate combined with other medications has generally favorable outcomes on hyperpigmentation, joint stiffness, and arthritis. In the most recent published article about the positive effect of mycophenolate mofetil on some clinical manifestations of H syndrome especially cutaneous stiffness and the surrounding joints dysmotility, the authors found that this therapy could have very promising results.[21]

In Table 1, the rows are the common symptoms of H syndrome that previous studies reported differences after receiving treatment. It is important to note that some of the common symptoms of H syndrome were not included in this table since there are no reported treatment on effects of medications on these conditions such as cardiac anomalies and hepatosplenomegaly. For hearing loss, no treatment is reported (patients are accustomed to using a hearing aid), while also not any reports are available regarding the halting progression of this condition during therapy. The hypertrichosis has almost permanent treatment as hair removal laser.

Conclusion

H syndrome does not have any standard treatment for preventive and therapeutic approach toward its cutaneous and systemic presentations apart from hypertrichosis that could be almost permanently removed by laser. However, the latest findings suggest that there is possibility of prevention of short stature or other cutaneous and systemic complications in this syndrome with earlier diagnosis and treatment. So in this review, we evaluated and summarized proposed therapeutic options for H syndrome, for better disease management.

Acknowledgments

The authors would like to thank the Rasoul Akram Hospital Clinical Research Development Center (RCRDC) for its technical and editorial assists.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Molho-Pessach V, Lerer I, Abeliovich D, Agha Z, Abu Libdeh A, Broshtilova V, *et al.* The H syndrome is caused by mutations in the nucleoside transporter hENT3. Am J Hum Genet 2008;83:529-34.
2. Huber-Ruano I, Errasti-Murugarren E, Godoy V, Vera A, Andreu AL, Garcia-Arumi E, *et al.* Functional outcome of a novel SLC29A3 mutation identified in a patient with H syndrome. Biochem Biophys Res Commun 2012;428:532-7.
3. Meena D, Chauhan P, Hazarika N, Kansal NK. H syndrome: A case report and review of literature. Indian J Dermatol 2018;63:76-8.
4. Molho-Pessach V, Agha Z, Aamar S, Glaser B, Doviner V, Hiller N, *et al.* The H syndrome: A genodermatosis characterized by indurated, hyperpigmented, and hypertrichotic skin with systemic manifestations. J Am Acad Dermatol 2008;59:79-85.
5. Molho-Pessach V, Ramot Y, Camille F, Doviner V, Babay S, Luis SJ, *et al.* H syndrome: The first 79 patients. J Am Acad Dermatol 2014;70:80-8.
6. El-Khateeb EA. The H syndrome. Pediatr Dermatol 2010;27:65-8.
7. Spiegel R, Cliffe ST, Buckley MF, Crow YJ, Urquhart J, Horovitz Y, *et al.* Expanding the clinical spectrum of SLC29A3 gene defects. Eur J Med Genet 2010;53:309-13.
8. Razmyar M, Rezaieyazdi Z, Tayebi Meibodi N, Fazel Z, Layegh P. H syndrome masquerade as rheumatologic disease. Int J Pediatr 2018;6:7965-71.
9. Nasimfar A, Sanaei Dashti A, Haghbin H. A child with H syndrome. Arch Pediatr Infect Dis 2016;4:e28321.
10. Bloom JL, Lin C, Imundo L, Guthery S, Stepenaskie S, Galambos C, *et al.* H syndrome: 5 new cases from the United States with novel features and responses to therapy. Pediatr Rheumatol Online J 2017;15:76.
11. De Benedetti F, Brunner H, Ruperto N, Schneider R, Xavier R, Allen R, *et al.* Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: Results from a phase III trial. Arthritis Rheumatol 2015;67:840-8.
12. de Jesus J, Imane Z, Senee V, Romero S, Guillausseau PJ, Balafrej A, *et al.* SLC29A3 mutation in a patient with syndromic diabetes with features of pigmented hypertrichotic dermatosis with insulin-dependent diabetes, H syndrome and Faisalabad histiocytosis. Diabetes Metab 2013;39:281-5.
13. Senniappan S, Hughes M, Shah P, Shah V, Kaski JP, Brogan P, *et al.* Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) syndrome is associated with severe chronic inflammation and cardiomyopathy, and represents a new monogenic autoinflammatory syndrome. J Pediatr Endocrinol Metab 2013;26:877-82.
14. di Dio F, Mariotti I, Coccolini E, Bruzzi P, Predieri B, Iughetti L. Unusual presentation of Rosai-Dorfman disease in a 14-month-old Italian child: A case report and review of the literature. BMC Pediatr 2016;16:62.
15. Moynihan LM, Bundey SE, Heath D, Jones EL, McHale DP, Mueller RF, *et al.* Autozygosity mapping, to chromosome 11q25, of a rare autosomal recessive syndrome causing histiocytosis, joint contractures, and sensorineural deafness. Am J Hum Genet 1998;62:1123-8.
16. Prendiville J, Rogers M, Kan A, de Castro F, Wong M, Junker A, *et al.* Pigmented hypertrichotic dermatosis and insulin dependent diabetes: Manifestations of a unique genetic disorder? Pediatr Dermatol 2007;24:101-7.
17. Elbarbary NS, Tjora E, Molnes J, Lie BA, Habib MA, Salem MA, *et al.* An Egyptian family with H syndrome due to a novel mutation in SLC29A3 illustrating overlapping features with pigmented hypertrichotic dermatosis with insulin-dependent diabetes and Faisalabad histiocytosis. Pediatr Diabetes 2013;14:466-72.
18. Kismet E, Koseoglu V, Atay AA, Deveci S, Demirkaya E, Tuncer K. Sinus histiocytosis with massive lymphadenopathy in three brothers. Pediatr Int 2005;47:473-6.
19. Mistry A, Parry D, Matthews B, Laws P, Goodfield M, Savic S. A case of SLC29A3 spectrum disorder-unresponsive to multiple immunomodulatory therapies. J Clin Immunol 2016;36:429-33.
20. Fujita E, Komine M, Tsuda H, Adachi A, Murata S, Kamata Y, *et al.* Case of H syndrome with massive skin involvement, retroperitoneal fibrosis and Raynaud's phenomenon with a novel mutation in the SLC29A3 gene. J Dermatol 2015;42:1169-71.
21. Behrangi E, Sadeghzadeh-Bazargan A, Khosravi S, Shemshadi M, Youssefian L, Vahidnezhad H, *et al.* Mycophenolate mofetil treatment of an H syndrome patient with a SLC29A3 mutation. Dermatol Ther 2020;33:e14375.