# Hereditary spherocytosis misdiagnosed as severe thalassemia for more than two decades: A case report

Somchai Insiripong, M.D.*, Watcharin Yingsitsiri, M.D.*,
Juree Boondumrongsakul, M.D.*, Jirawadee Noiwanakul, M.D.*

**Abstract:** The patients with hereditary spherocytosis (HS) mostly have mild degree of hemolytic anemia, mild jaundice and splenomegalyand usually respond well to splenectomy. In occasional instances, the diagnosis of HS may be overlooked and delayed for a very long time as in our case. She was a 26-year-old Thai patient who was simply diagnosed as severe thalassemia since childhood because of her typical thalassemicfacy, severe microcytic hemolytic anemia, the prominent splenomegaly and herbirth placewhere various thalassemias and hemoglobinopathies were highly prevalent. She had been treated with regular blood transfusion every two or three months since then. The splenectomy and later cholecystectomy were performed at the age of 9 and 12 years old, respectively. The last blood test showed Hb 9.4 g%, Hct 25.3%, MCV 77.2 fL, MCHC 37.0, RDW 21.5%, hypochromia 1+, microspherocytosis 2+, ferritin 4,142-5,611 ng/mL. With repeated Hb electrophoresis, slightly increased percentage of Hb $A_2$, 3.7-4.4 %, was the only one abnormality detected. Other blood tests included positive osmotic fragility test, negative direct anti-globulin test. The thalassemia genotype study revealed only alpha-thalassemia-2 (3.7 kb) trait, neither alpha thalassemia-1 nor beta thalassemia genotype was found, therefore the final diagnosis of severe HS with secondary hemosiderosiswas established. The slightly increased percentage of Hb $A_2$ overlapping thatof beta thalassemia trait was presumably due to severe HS itself. Likewise, the so-called thalassemicfacy in our case was supposedlyfrom the active intramedullary erythropoiesis compensating to severe and chronic hemolysis since birth that could be documented in any case with either severe thalassemia or severe HS.

* Hematology Unit, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000

**บทคัดย่อ: Hereditary spherocytosis ที่ได้รับการวินิจฉัยคลาดเคลื่อนว่าเป็นธาลัสซีเมียรุนแรงนานกว่า 2 ทศวรรษ: รายงานผู้ป่วย 1 ราย**

สมชาย อินทรศิริพงษ์, พ.บ.*, วัชรินทร์ ยิ่งสิทธิ์สิริ, พ.บ.*,
จุรี บุญดำรงสกุล, พ.บ.*, จิราวดี น้อยวัฒนกุล, พ.บ.*
* หน่วยโลหิตวิทยา, โรงพยาบาลมหาราชนครราชสีมา, จังหวัดนครราชสีมา 30000
*เวชสารโรงพยาบาลมหาราชนครราชสีมา 2560; 39: 119-124.*

ผู้ป่วย hereditary spherocytosis (HS) ส่วนมากมีอาการ hemolytic anemia ที่ไม่รุนแรง, มีดีซ่านเล็กน้อย และม้ามโต และมักตอบสนองดีต่อการตัดม้ามในบางสถานการณ์ HS อาจถูกมองข้ามและไม่ได้รับการวินิจฉัยเป็นเวลานาน ๆ ได้แบบผู้ป่วยรายนี้ได้ซึ่งเป็นหญิงไทย อายุ 26 ปี ได้รับการวินิจฉัยอย่างง่าย ๆ ว่าเป็นธาลัสซีเมียรุนแรงตั้งแต่เด็ก เพราะการเปลี่ยนแปลงของใบหน้าและกะโหลกศีรษะเป็นแบบจำเพาะที่เรียกว่า ใบหน้าแบบธาลัสซีเมียร่วมกับ microcytic hemolytic anemia ขั้นรุนแรง ม้ามโตอย่างเด่นชัด และถือกำเนิดในเขตที่มีธาลัสซีเมีย และฮีโมโกลบินผิดปกติชุกชุม ได้รับเลือดประจำทุก 2 หรือ 3 เดือนมาเรื่อย ๆ ได้รับการตัดม้าม และถุงน้ำดีเมื่ออายุได้ 9 และ 12 ขวบ ผลเลือดครั้งล่าสุดพบว่า Hb 9.4 g%, Hct 25.3%, MCV 77.2 fL, MCHC 37.0, RDW 21.5 %, hypochromia 1+, microspherocytosis 2+, ferritin 4,142-5,611 นาโนกรัม/มล ตรวจแยกชนิดของฮีโมโกลบิน หลายครั้งก็พบเพียง Hb $A_2$ เพิ่มขึ้นเพียงเล็กน้อยระหว่าง 3.7-4.4 % การทดสอบ osmotic fragility ให้ผลบวก, direct anti-globulin test ให้ผลลบ ตรวจยีนส์ธาลัสซีเมียพบเพียง alpha-thalassemia-2 (3.7 kb) แฝงเท่านั้น ไม่พบทั้ง alpha thalassemia-1 และเบต้าธาลัสซีเมียแฝง จึงสรุปการวินิจฉัยโรคเป็น HS แบบรุนแรง มีภาวะเหล็กเกินทุติยภูมิ การที่ผู้ป่วยมีสัดส่วนของ Hb $A_2$ เพิ่มขึ้นเล็กน้อยแบบเดียวกับที่พบในผู้ที่มีเบต้าธาลัสซีเมียแฝง เชื่อว่าเป็นผลจากโรค HS รุนแรงโดยตรง และก็เช่นเดียวกันหน้าตาแบบธาลัสซีเมียที่พบในผู้ป่วยรายนี้ เชื่อว่าน่าจะเกิดจากการสร้างเม็ดเลือดในโพรงไขกระดูกที่เพิ่มขึ้นมากเพื่อชดเชยการที่เม็ดเลือดแดงแตกรุนแรง และเรื้อรังตั้งแต่แรกเกิด ซึ่งเป็นภาวะที่พบได้ทั้งในธาลัสซีเมียที่รุนแรง และ HS ที่รุนแรงเช่นกัน

**Introduction**

Hereditary spherocytosis (HS) is a genetic disorder resulting in the defects of some proteins of the cell membrane of red blood cells (RBC), ankyrin, band -3, protein 4.2 or spectrin. This leads to loss of the membrane surface area, to form the spherocytethat will be trapped and destroyed in the spleen, causing hemolysis and splenomegaly. The main presentations consist of hemolytic anemia, mild jaundice and splenomegaly and the severity of anemia is extremely variable. Most cases have a well-compensated hemolytic anemia while the minority have severe anemia until RBC transfusion is needed[1].

The RBC in HS is characterized by lack of the central pallorand typical RBC indices consisting of decreased mean corpuscular volume (MCV) and increased mean corpuscular hemoglobin concentration (MCHC)[2].

HS is common in the north European popu-lation but rather rare in oriental countries such as, Thailand[3], Japan[4] and Malaysia[5]. Atypical cases of HS may be easily misdiagnosed[6] especially in the patient with severe hemolytic anemia born in Nakhon Ratchasima, the area of the highest prevalence of thalassemia/ hemoglobinopathy[7]. This report was aimed to study and discussthe case of severe HS whose proper diagnosis was overlooked and delayed for more than two decades.

**Case Report**

A 26-year old Thai married woman had been misdiagnosed as severe thalassemia since early childhood because of severe hemolytic anemia with hypochromia andmicrocytosis, and the typicalthalassemicfacy, frontal bossing, saddle nose and maxillary protrusion, prominent upper incisor. She was regularly transfused with the packed RB Cevery 2 or 3 months since then. The splenectomy due to too frequent transfusion at the age of 9 years and the cholecystectomy because of gall stones cholecystitis with the were performed at the age of 12 years old.

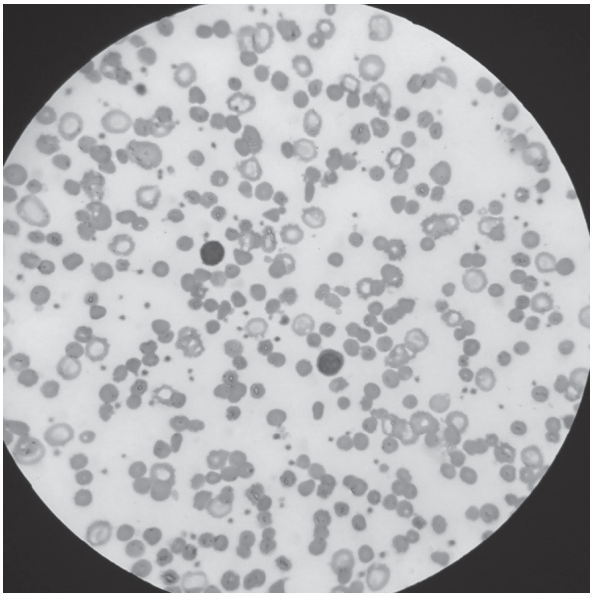
Her weight was 45 kg, height was 1.65 m. and BMI was 16.5 kg/m$^2$. Besides the thalassemicfacy, she had pallor, mild jaundice, generalized dark skin but no hepatomegaly. The last CBC: Hb 9.4 g%, Hct 25.3%, MCV 77.2 fL, MCH 28.6 pg, MCHC 37.0 g%, RDW 21.5%, WBC 19,200/mm$^3$, platelet 781,000/mm$^3$, hypochromia 1+, few anisocytosis 2+, microcytosis 2+, spherocytosis 2+.

Other tests: creatinine 0.5 mg%, albumin 3.7 g%, globulin 4.0 g%, direct bilirubin 0.9 mg%, total bilirubin 4.7 mg%, uric acid 3.7 mg%, erythropoietin 167 mIU/mL (normal 2.6-34.0), ESR 54 mm/hr, ferritin 4,142-5,611 ng/mL, serum iron 148 mcg% (normal 35-165), TIBC 321 mcg% (normal 259-388), FBS 100 mg%.

The repeated Hbelectrophoresis using the high performance liquid chromatography (Bio-Rad®) showed Hb A2A, Hb F 1.3-2.1%, Hb A2 3.7-4.4%, the thalassemia genotype study showed no common and rare beta-thalassemia, no alpha-thalassemia-1 (SEA and Thai deletions) but alpha-thalassemia-2 genes (3.7 kb deletion) detected.

Other hemolytic tests: negative direct anti-globulin test, positive osmotic fragility test, normal G-6-PD enzyme, negative Ham's test, no urine he-mosiderin. The flow cytometry showed no clone of paroxysmal nocturnal hemoglobinuria.

Her final diagnosis was severe HS, secondary hemosiderosis and alpha-thalassemia-2 trait. And she still has been receiving the blood transfusion every 2 or 3 months with deferiprone.



The pedigree could not be studied, her parents passed away in the traffic accident. She had no sibling and no offspring the birth control.

**Discussion**

Our case has been misdiagnosed as severe thalassemia for more than 2 decades because of the typical thalassemic or chipmunk facy[8] in combination with microcytic hemolytic anemia. With familiarity, all cases with such microcytic hemolytic anemia found in Thailand are expected to have one of thalassemia and/or hemoglobinopathy[9,10] although the Hbelectrophoresishas never detected any severe form of thalassemia.

The misdiagnosis as severe thalassemia has been continued after the splenectomy because the Hb concentration is not dramatically improved that seems more consistent with the characteristic of severe beta thalassemia or beta-thalassemia / Hb E disease whereas it can be normalized in most patients with HS[11], except the patients who have the spectrin less than 30-74 %[12] or the severe form of HS[13] that may respond only slightly to splenectomy.

Her final diagnosis of severe HS is definitely made after the full investigations of the hemolytic ane-mia show positive osmotic fragility test that has sensi-tivity ranging from 48 to 95 % for the diagnosis[14], with the typical RBC indices; low MCV, high MCHC and high RDW although the new generation tests such as the eosin-52-maleimide-binding test, the acidified glycerol lysis test or pink test has not been performed yet[15].

The mean MCHC among cases with HS was 35.7±1.3 g% while the RDW was 20.6±4.5 % and 70 % of caseshave MCHC more than 38 g%. The combination of MCHC >34.5 g% and RDW >14.5 % have sensitivity 81 % and specificity 98 % for the diagnosis of HS[16]. Some authorsadded MCV <80 fl upon the combination of MCHC > 38 g% and RDW > 15 % forsuggesting HS[17]. The RBC indices in our case consisted of MCV 77.2 fL, MCHC 37.0 g% and RDW 21.5%. Not only they did not oppose but also support the diagnosis of HS.

The percentage of Hb $A_2$ was slightly increased in our case for many times, 3.7-4.4%, almost overlap-ping the range of Hb $A_2$ of beta thalassemia trait (BTT), 4.2-8.2 %[18]. Besides the misdiagnosis as a severe thalassemia, the slightly higher Hb $A_2$ also misleads us to diagnose BTT with marked anemia from unknown etiologies until the beta thalassemia genotypes was proved to be absent. It seems to suggest that slightly increased Hb $A_2$ may be directly due to HS itself[19]. Likewise, the so-called typical thalassemicfacy could be found in not only severe thalassemia[18,20] but also in other congenital severe and long standing hemolytic anemia with the intra-medullary erythroid hyperpla-sia[21] for compensation such as Gaucher's disease[22]. On the contrary, the thalassemia facy in cases with severe thalassemia may be prevented by the adequate transfusion[23].

Because BTT is highly prevalent, 1.7-6.0 %, in Thailand[7], when the normal or mildly anemic patients with low MCV and slightly high Hb $A_2$ level are encountered, the diagnosis of BTT is almost definitely concluded and HS will be easily overlooked. However the MCHC may be helpful to distinguish these two easily confusing entities because it is definitely different, 31.1+2.2 in BTT[24] vs 35.7±1.3 g% in HS.

**Acknowledgement**

Assoc. Prof. Dr.Supan Fucharoen, Faculty of Associated Medical Sciences. Khonkaen University, for thalassemia genotyping study.

## Conclusion

A 26-year-old Thai woman was misdiagnosed as severe thalassemia for more than two deacades because of transfusion-dependent microcytic hemo-lytic anemia with typical thalassemicfacy. Based on the MCV 77.2 fl, MCHC 37.0 g%, RDW 21.5 %, positive osmotic fragility and only slightly increased Hb $A_2$ concentration, the final diagnosis was corrected to be severe hereditary spherocytosis.

## References


1. Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis Lancet 2008; 372: 1411-26. doi: 10.1016/S0140-6736(08)61588-3.
2. Bolton-Maggs PHB, Stevens RF, Dodd NJ, Lamont G, Tittensor P, King M-J. Guidelines for the diagnosis and management of hereditary spherocytosis. Br J Haematol 2004; 126: 455-74.
3. Panich V, Wasi P, Na-Nakorn S. Hereditary spherocytosis in Thailand. Clinical, hematologic and genetic studies. J Med Assoc Thai 1970; 53: 179-89.
4. Yawata Y, Kanzaki A, Yawata A, Doerfler W, Ozcan R, Eber SW. Characteristic features of the genotype and phenotype of hereditary spherocytosis in the Japanese population. Int J Hematol 2000; 71: 118-35.
5. Sheikh MK, Yusoff NM, Kaur G, Khan FA. Hereditary spherocytosis in a Malay patient with chronic haemolysis. Malays J Med Sci2007; 14: 54-7.
6. Deng Z, Liao L, Yang W, Lin F. Misdiagnosis of two cases of hereditary spherocytosis in a family and review of published reports. Clin Chim Acta 2015; 441: 6-9. doi:10.1016/j.cca.2014.12.002. Epub 2014 Dec 6.
7. วิชัย เทียนถาวร, จินตนา พัฒนพงศ์ธร, สมยศ เจริญศักดิ์, รัตน์ติกา แซ่ตั้ง, พิมพ์ลักษณ์ เจริญขวัญ, ต่อพงศ์ สงวนเสริมศรี. ความชุกของพาหะธาลัสซีเมียในประเทศ. ไทยวารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2549; 16: 307-12.
8. Hattab FN. Periodontal condition and orofacial changes in patients with thalassemia major: a clinical and radiographic overview. J ClinPediatr Dent 2012 Spring; 36: 301-7.
9. Marotti J, Bryan B, Bhargava P. Mild anemia, microcytosis, and target cells in a man from Thailand. Lab Med 2007; 38: 539-42.
10. Fucharoen S, Weatherall DJ. The hemoglobin E thalassemias. Cold Spring Harb Perspect Med 2012; 2(8): a011734. doi: 10.1101/cshperspect.a011734.
11. Gallagher PG. Red cell membrane disorders. Hematology, Am Soc Hematol Educ Program 2005: 13-8.
12. Agre P, Asimos A, Casella JF, McMillan C. Inheritance pattern and clinical response to splenectomy as a reflection of erythrocyte spectrin deficiency in hereditary spherocytosis. N Engl J Med 1986; 315: 1579-83.
13. Eber SW, Armbrust R, Schroter W. Variable clinical severity of hereditary spherocytosis: relation to erythrocyte spectrin concentration, osmotic fragility, and autohemolysis. J Pediatr 1990; 117: 409-16.
14. Mariani M, Barcellini W, Vercellati C, Marcello AP, Fermo E, Pedotti P, et al. Clinical and hematologic features of 300 patients affected by hereditary spherocytosis grouped according to the type of the membrane protein defect. Haematologica 2008; 93: 1310-7.
15. Bianchi P, Fermo E, Vercellati C, Marcello AP, Porretti L, Cortelezzi A, et al. Diagnostic power

of laboratory tests for hereditary spherocytosis: a comparison study in 150 patients grouped according to molecular and clinical characteristics. Haematologica 2012; 97: 516-23.

16. Eberle SE, Sciuccati G, Bonduel M, Diaz L, Staciuk R, Torres AF. Erythrocyte indexes in hereditary spherocytosis. Medicina (B Aires) 2007; 67: 698-700.
17. Barbullushi A, Daja P, Bali D, Maliqari N, Godo A. Hereditary spherocytosis and red cell indices MCHC, MCV, RDW. Arch Dis Child 2014; 99: A143 doi:10.1136/ archdischild-2014-307384.384.
18. Khera R, Singh T, Khuana N, Gupta N, Dubey AP. HPLC in characterization of hemoglobin profile in thalassemia syndromes and hemoglobinopathies: A clinicohematological correlation. Indian J Hematol Blood Transfus 2015; 31: 110-5.
19. Harmeling JG, Moquin RB. An abnormal elevation of hemoglobin A2 in hereditary spherocytosis. Am J Clin Pathol 1967; 47: 454-8.
20. Elangovan A, Mungara J, Joseph E, Guptha V. Prevalence of dentofacial abnormalities in children and adolescents with â-thalassaemia major. Indian J Dental Res 2013; 24: 406-10.
21. Sherwani P, Vire A, Anand R, Gupta R. Lung lysed: A case of Gaucher disease with pulmonary involvement. Lung India 2016; 33: 108-10.
22. Gürakan F, Koçak N, Yüce A, Ozen H. Gaucher disease type I: analysis of two cases with thalassemicfacies and pulmonary arteriovenous fistulas. Turk J Pediatr 2001; 43: 237-42.
23. Tubman VN, Fung EB, Vogiatzi M, Thompson AA, Rogers ZR, Neufeld FJ, et al. Guidelines for the standard monitoring of patients with thalassemia: Report of the thalassemia longitudinal cohort. J Pediatr Hematol Oncol 2015; 37: e162-9.
24. Hussain Z, Malik N, Chughtai AS. Diagnostic significance of red cell indices in beta thalassemia trait. Biomedica 2005; 21: 129-31.