Incidence and Risk Factors of Relapses in Idiopathic Autoimmune Hemolytic Anemia

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Background: *Patients with idiopathic autoimmune hemolytic anemia (AIHA) of warm antibody type usually respond to corticosteroid therapy. However, a proportion of patients will have disease relapse after steroid-induced remission.*

Objective: *To assess the incidence and the possible risk factors of the relapse in a cohort of patients with idiopathic AIHA.*

Material and Method: *We conducted a retrospective and prospective study of 34 idiopathic AIHA patients regularly followed at the Division of Hematology during January 1973 to December 2006. The medical records were reviewed for active hemolytic events and relapses, episodes of infections, pattern of corticosteroids administration and tapering. Types and subtypes of autoantibodies were studied by column agglutination test (the "gel test").*

Results: *One patient with cold agglutinin disease was excluded, leaving a total of 33 patients (24 with warm type, 9 with mixed warm and cold type AIHA) in the study. The incidence of relapse was 1.157 episodes/person/year. The mean duration of relapse after remission was 23 months. Episodes of recurrent hemolysis were more frequent when corticosteroid administration was tapered from high to low dose (10 mg/day of prednisolone) within two months compared with a longer than two-month tapering (38 vs. 11 episodes; $p < 0.01$). In addition patients receiving continuing low dose of corticosteroids ($\leq$ 10 mg/day of prednisolone) for > 6 months had lower incidence of relapse and longer duration of remission than those with discontinuing the medication within 6 months (0.443 vs. 1.911 episodes/person/year, $p < 0.01$; 37.4 vs. 10.6 months, $p < 0.01$). Episodes of recurrent hemolysis were more frequently observed in patients with events of infection than those without infections (mean 7.69 vs. 2.81, $p = 0.032$). Types and subtypes of autoantibodies did not seem to influence relapse in AIHA.*

Conclusion: *Short duration of maintenance and rapid tapering of corticosteroids and infections are possible risk factors of relapses/recurrent hemolysis in idiopathic AIHA.*

Keywords: *Autoimmune hemolytic anemia, Incidence of relapse, Corticosteroids*

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Autoimmune hemolytic anemia (AIHA) is characterized by hemolytic anemia due to autoantibody-induced clearance of the of the patients' own red cells. It can be classified according to the optimal temperature of antigen-binding of the causative antibody into the warm (antibody) type and cold (antibody) type AIHA; with maximal reactivities of the autoantibodies to red blood cells at 37°C and 4°C, respectively. In Thailand, warm type AIHA is far more common than the disease with cold reactive autoantibody[1]. Both types of AIHA may occur without apparent etiology (primary or idiopathic AIHA) or following other diseases (secondary AIHA). Corticosteroids remain the standard treatment, leading to correction of the anemia in the patients with warm (antibody) type AIHA[2]. However, permanent remission after corticosteroids was observed in only 20-35% of patients with AIHA[3]. Many patients exhibit relapses of hemolytic anemia during corticosteroids tapering or after discontinuation of this

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medication.

It is unclear what factors are responsible for the relapses in AIHA. Infective episodes[4], stress, rapid reduction of corticosteroids[5] have been suggested, without sufficient support, as precipitating factors of reactivation of the hemolytic anemia. We have observed a variation in regimens of corticosteroid reduction, among clinicians, after the initial responses to the standard doses of 60-80 mg/day of prednisolone (prednisone) in patients with warm type AIHA followed at our institution. Obviously, identification of risk factors of relapses among the patients with AIHA will prevent such episodes and avoid side effects from unnecessary exposure to high doses and long term administration of corticosteroids. We, therefore, studied the incidence of relapses in patients with idiopathic AIHA and explored the possible risk factors responsible for the relapses and also the recurrent (active) hemolysis in the disease, especially infections and the pattern of steroids tapering.

Material and Method

Study design

This study is descriptive, consisting of retrospective review of medical records and prospective follow-up of the clinical courses of the patients with idiopathic autoimmune hemolytic anemia (AIHA) followed at the Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University. The study was approved to be done by the Faculty ethic committee and informed consents were obtained from all patients.

Patients

Patients diagnosed as idiopathic AIHA who had been regularly followed at the hematology clinic of the Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, between January 1973 and December 2006, were screened to participate in the study. Eligible criteria included: a) patients who were diagnosed warm type AIHA without associated diseases (idiopathic AIHA) or other cytopenias, b) those who could be regularly followed (every 2-3 months) during the study period of one year. A total of 34 patients with idiopathic autoimmune hemolytic anemia were initially enrolled in the study. One patient was found to have cold type AIHA (cold agglutinin disease) and was subsequently excluded, leaving 33 patients with idiopathic warm type AIHA included in the study.

During each visit, three milliliter of blood was drawn in an ethylene-diamine-tetra-acetic acid (EDTA) tube from each patient for complete blood count (CBC) and direct Coombs' test and for detection of RBC-bound immunoglobulins (Igs) and complement (C) by the gel test for the first visit or during a visit with active hemolysis episode (see "Definition").

Methods

A. Detection of RBC-bound Immunoglobulins (Igs) and complement (C)

Red cell bound IgG and its subclass IgG1 and IgG3, IgM, IgA, and C (C3c and C3d) were detected by the gel test (DiaMed, Switzerland) using relevant monospecific anti-human globulins at the first time of study or during an episode of active hemolysis. Briefly, 50 µl of 1% red blood cell suspension were applied to microtubes containing monospecific anti-human globulins on gel. After centrifugation of the micro-tubes, specific RBC bound Igs (IgG, IgG1, IgG3, IgM, IgA) and C (C3c and C3d) were identified by observation of agglutination in the micro-tubes containing corresponding monospecific anti-human globulins.

B. Review of medical records

The medical record of each patient was reviewed for episodes of relapse and recurrent (active) hemolysis (see "Definition"), episodes of infections, duration and pattern of corticosteroids tapering off.

C. Prospective follow-up

Patients were clinically and laboratory evaluated for recurrent (active) hemolysis or relapses (see "Definition"). Inter-current infections were also assessed, based on history of recent fever, symptoms and signs suggested sources of infections and in some patients, microbiological evidences.

Definition

A. Disease remission

Status when hemoglobin (Hb) concentration >10 g/dL, without evidence of hemolysis for more than 3 months and while receiving less than 10 mg/day of prednisolone).

B. Relapse

Status following a remission when the patient's Hb concentration falls below 10g/dL.

C. Recurrent hemolysis

Status of increasing anemia (Hb < 10g/dL if previously > 10g/dL; or a decrease of Hb level at least

> 1g/dL) as a result of autoimmune hemolysis (positive direct Coombs' test and hemolytic blood picture or biochemical evidences of hemolysis).

Statistical analysis

Statistical analysis was performed using SPSS program. Results are expressed as means and percentages. Chi-square test was used for comparison of variables and significant difference was recognized when a p-value was less than 0.05.

Results

Patients' profiles and red cell autoantibody

A total of 34 patients with idiopathic AIHA were initially included in the study. One patient with cold type AIHA was excluded leaving 33 patients in the study, there were 29 females and 4 males with an age range and mean of 15-77 and 41years, respectively. The follow-up duration was 1-33 years. Of the 33 patients, 24 (73%) and 9 (27%) patients had warm type and mixed warm and cold type AIHA, respectively.

With the gel test, the most common red cell autoantibody was IgG + C3 (57%), especially IgG1 + C3d (40%). IgG + IgM + C3, IgG alone and C3 alone were detected in 20%, 6.7% and 6.7%, respectively. The most common IgG subclass was IgG1 (67%), alone or with associated IgG3 (10%) (Table 1).

Table 1. Pattern of red cell bound immunoglobulins (Igs) and complement (C)

Red cell bound Igs/C	No. of patients (%)
IgG (IgG_1), C3d	12 (40)
IgG ($nonlgG_1$, $nonlgG_3$), C3d	3 (10)
IgG ($nonlgG_1$, $nonlgG_3$), IgM, C3d	2 (6.7)
IgG (IgG_1)	2 (6.7)
C3d	2 (6.7)
IgG (IgG_1, IgG_3), IgM, C3d	1 (3.3)
IgG (IgG_1), IgA, IgM, C3c, C3d	1 (3.3)
IgG (IgG_1), IgM, C3c, C3d	1 (3.3)
IgG ($nonlgG_1$, $nonlgG_3$)	1 (3.3)
IgG (IgG_1), C3c, C3d	1 (3.3)
IgG (IgG_1, IgG_3), IgM, C3c, C3d	1 (3.3)
Positive all	1 (3.3)
Negative all	2 (6.7)
Total	30 (100)

Incidence of recurrent hemolysis and relapses

During the follow-up periods of the 33 patients, there were 159 and 100 episodes of recurrent hemolysis and relapses, respectively. The calculated incidence was 1.157 relapses/patient/year. The average time from disease remission to relapse was 23 months, with 168 months as the longest and immediately after disease remission as the shortest. Types of AIHA, class and subclass of autoantibodies or complement did not seem to influence the relapse rate.

Factors determining recurrent hemolysis and relapses

A. Effect of duration of corticosteroid tapering on recurrent hemolysis

We observed two different patterns (duration) of corticosteroids tapering after initial response to the starting doses of 1 mg/kg/day of prednisolone. We found that a shorter duration of corticosteroid tapering from high starting dose (1 mg/kg/day) to the usual low maintaining dose (10 mg/day) determined recurrent hemolysis. Patients who underwent less than two months of tapering had significantly more episodes of recurrent hemolysis within two months after tapering than those with longer tapering periods ($p < 0.01$) (Table 2).

B. Infections and recurrent hemolysis

Of the 33 patients, 12 exhibited more than one episode of infection, during the follow-up periods, while the other 21 patients attended our clinic during follow-ups with no complaints or evidences of infections. We could not directly relate the episodes of infections with those of recurrent hemolysis. However we found that patients with frequent infections had more average episodes of recurrent hemolysis than those without infection (7.69 vs. 2.81, $p = 0.032$) (Table 3).

C. Duration of corticosteroid maintenance and relapses

After remission, a number of patients were maintained with low dose of corticosteroids for different durations. We found that maintenance with 10 mg/day of prednisone or lower for at least 6 months led to longer periods of remission and lower frequency or incidence of relapse than those maintained for shorter durations of the low-dose corticosteroids (Table 4).

Discussion

In this study, the distribution of the types of AIHA in Thailand based on the optimal temperature of antibody binding to autologous red blood cells as well as the pattern of red cell bound immunoglobulins and complements, were more or less the same as the previ-

Table 2. Effect of duration of corticosteroid tapering on recurrent hemolysis

Time of corticosteroid tapering (from starting dose to 10 mg/day)	Number of episodes of recurrent hemolysis		
	Recurrences within 2 months (after tapering)	Recurrences after 2 months (after tapering)	All recurrences
< 2 months	38 (23.9%)[a]	48 (30.2%)	86 (54.1%)
≥ 2 months	11 (6.9%)[a]	62 (39%)	73 (45.9%)
Total	49 (30.8%)	110 (69.2%)	159 (100%)

a: $p < 0.01$

Table 3. Infections and episodes of recurrent hemolysis

Group of patients according to evidences of infections	Number of episodes of recurrent hemolysis(mean)[a]
Without evidence of infection (n = 21)	2.81
With evidences of infections (n = 12)	7.69

a: $p = 0.032$

Table 4. Effects of duration of corticosteroid maintenance on frequency of relapse and periods (durations) of remission

Duration of corticosteroid maintenances	Number (No.) of relapses	Frequency of relapse (No./ patient/year)*	Periods of remission (months)*
≤ 6 months	54	1.91 ± 0.32^a	10.61 ± 1.92^b
> 6 months	46	0.44 ± 0.08^a	37.38 ± 4.88^b

* Mean ± SEM; a: $p < 0.01$; b: $p < 0.01$

ous report[1]. Cold type AIHA (cold agglutinin disease) was uncommon, while mixed warm and cold type was found in 27% and 30% in our study and in the previous report from Thailand[1], respectively. We exclude the patient with cold type AIHA from our study as the nature of the disease is different from the warm type AIHA.

As with other autoimmune disorders, recurrence of active disease and relapse after remission are quite common in AIHA. Although 80% of patients with warm type AIHA have a good initial response to treatment with corticosteroids[6], only 20-35% of them acquire permanent remission[3]. More than 50% of patients had recurrent hemolysis or relapses after the initial response to corticosteroids[7]. Infective episodes[4], stress, pregnancy, rapid reduction of corticosteroids[5] have been suggested as precipitating factors of reactivation of the hemolytic anemia in AIHA. Many hematologists suggest a gradual tapering of corticosteroids to prevent recurrent active hemolysis in AIHA[8].

In this study, we demonstrated the episodes of recurrence of active disease in two phases, *i.e.*, during corticosteroid tapering and when the disease was in remission (see "Definition") We found 159 episodes of recurrent active hemolysis during corticosteroid tapering and 100 episodes of relapses after the disease was inactive, with an incidence of 1.157 relapses/patient/year. The longest duration of relapse was 168 months after disease remission. Patients who were subjected to rapid tapering of corticosteroids from the high starting dose (1 mg/kg/day) to the low maintenance dose of 10 mg/day within two months had a significantly higher rate of recurrence of active hemolysis than those with more gradual dose reduction (Table 2). However, prolongation of tapering period up to three months did not result in a higher recurrent rate than the longer (more than three months) tapering (data not shown). Our findings suggest and support the concept of gradual reduction of corticosteroid dosage after the initial response[9], for example once the anemia has been corrected, the usual initial dose of 60 mg/day of prednisolone is reduced at a rate of 10 mg/day every week until at 30 mg/day, then at a slower rate of 5 mg/day every week, to a dose of 15-20 mg/day. Prednisolone should be maintained at this dose for 2-3 months before further reduction to 10 mg/day for a few months before cessation.

After remission, patients who received longer than six-month maintenance of low dose corticosteroids (≤ 10 mg/day of prednisolone) had lower frequency of disease relapse and longer duration of remission than those receiving shorter period of maintenance. However, the decision to maintain corticosteroids for

such a long period of time should be balanced by awareness of their side effects[10]. The once-daily and alternate-day schedule at this dosage is believed to reduce glucocorticoid side effects.

We could not directly demonstrate the precipitating effect of infections on relapses in AIHA. However, the findings that patients with frequent episodes of infections had higher frequency of recurrent hemolysis than those with hardly any infective episodes, suggested that infection is a possible precipitating factor of active hemolysis in AIHA[4].

In conclusion, recurrence of active hemolysis and relapses are common in AIHA. Rapid tapering of corticosteroids and infections are the possible risk factors of recurrence of active hemolysis. Shorter maintenance period of corticosteroids is a possible risk factor of relapses in idiopathic AIHA.

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References

1. Kruatrachue M, Sirisinha S. Autoimmune hemolytic anemias in Thailand. Scan J Haematol 1997; 19: 61-7.
2. Petz LD. Treatment of autoimmune hemolytic anemia. Curr Opin Hematol 2001; 8: 411-6.
3. Zupanska B, Sylwestrowicz T, Pawelsky S. The results of prolonged treatment of autoimmune hemolytic anemia. Haematologica 1981; 4: 425-33.
4. Meite M, Leonard S, Idrissi ME, Masson PL, Coutelier JP. Exacerbation of autoantibody-mediated hemolytic anemia by viral infection. J Virol 2000; 74: 6045-9.
5. Rosse WF. Clinical Immunohematology: Basic Concepts and Clinical Applications. Boston: Blackwell Scientific, 1990.
6. Shulman I, Branch DR, Nelson JM, Thompson JC, Saxena S, Petz LD. Autoimmune hemolytic anemia with cold and warm autoantibodies. JAMA 1985; 253: 1746-8.
7. Liu H, Shao Z, Cui Z, Qin T, Fu R, *et al*. An analysis of relapse and risk factors of autoimmune hemolytic anemia and Evans syndrome. Zhonghua Xue Ye Xue Za Zhi 2003; 24: 534-7.
8. King KE, Ness PM. Treatment of autoimmune hemolytic anemia. Sem Hematol 2005; 42: 131-6.
9. Packman CH. Hemolytic anemia due to warm autoantibodies. Blood Rev 2008; 22: 17-31.
10. Lester RS, Knowles SR, Shear NHY. The risks of systemic corticosteroids use. Dermatol Clin 1998; 16: 277-88.

อุบัติการณ์และปัจจัยเสี่ยงของการกลับเป็นซ้ำของโรคโลหิตจางจากเม็ดเลือดแดงถูกทำลายโดยกลไกออโตอิมมูนชนิดไม่ทราบสาเหตุ

กุลวรา ดุษฎี, อรทัย ทะก่ำ, อัญชลี เทศสวัสดิ์, วันชัย วนะชิวนาวิน

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์ (incidence) และปัจจัยเสี่ยงที่มีผลต่อการกลับเป็นซ้ำของโรคโลหิตจางจากเม็ดเลือดแดงถูกทำลายโดยกลไกออโตอิมมูนชนิดไม่ทราบสาเหตุ (idiopathic autoimmune hemolytic anemia; AIHA) และที่ออโตแอนติบอดีจับกับเม็ดเลือดแดงได้ดีที่อุณหภูมิอุ่น (warm antibody type)*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงพรรณนาแบบย้อนหลัง และไปข้างหน้า (retrospective and prospective study) ของผู้ป่วย idiopathic AIHA จำนวน 34 ราย ที่มาติดตามรักษาระหว่าง มค. 2516 ถึง ธค. 2548 โดยการทบทวนจากรายงานผู้ป่วย และการติดตามผู้ป่วยในช่วงระยะเวลาการศึกษาไปข้างหน้าอย่างต่อเนื่องเป็นเวลา 1 ปี เพื่อดูการกลับเป็นซ้ำของภาวะโลหิตจาง (relapse) การกลับเป็นซ้ำของภาวะเม็ดเลือดถูกทำลาย (recurrent hemolysis) ภาวะติดเชื้อ รูปแบบของการลดยาคอร์ติโคสตีรอยด์ การศึกษาชนิดของออโตแอนติบอดีทำโดยวิธี column agglutination (gel test)*

ผลการศึกษา: *ได้ตัดผู้ป่วยออก 1 ราย เนื่องจากเป็นโรค cold agglutinin ทำให้มีผู้ป่วยในการศึกษา 33 ราย พบอุบัติการณ์ของการกลับเป็นซ้ำ 1.157 ครั้ง/คน/ปี โดยระยะเวลาเฉลี่ยของการกลับเป็นซ้ำหลังจากโรคสงบแล้ว (remission) 23 เดือน พบการกลับเป็นซ้ำของภาวะเม็ดเลือดแดงถูกทำลาย (recurrent hemolysis) ในผู้ป่วยที่มีการลดคอร์ติโคสตีรอยด์จากขนาดที่สูงจนถึงขนาดที่ต่ำ (เท่ากับ 10 มก/วัน ของยา prednisolone) เร็ว (ในเวลา 2 เดือน) มากกว่าผู้ป่วยที่ได้รับการลดขนาดของยาที่ช้ากว่า (38 ครั้งต่อ 11 ครั้ง; $p < 0.01$) นอกจากนี้ผู้ป่วยที่ได้รับคอร์ติโคสตีรอยด์ในขนาดต่ำ (prednisolone ขนาดเท่ากับหรือน้อยกว่า 10 มก/วัน) เป็นเวลานานกว่า 6 เดือน จะมีอุบัติการณ์ของการกลับเป็นซ้ำ (relapse) น้อยกว่า (0.443 ครั้ง/คน/ปี เทียบกับ 1.911 ครั้ง/คน/ปี; $p < 0.01$) และระยะเวลาที่โรคสงบยาวนานกว่า (37.4 เดือนเทียบกับ 10.6 เดือน; $p < 0.01$) เมื่อเทียบกับผู้ป่วยที่ได้รับยาในขนาดต่ำน้อยกว่า 6 เดือน พบการกลับเป็นซ้ำของภาวะเม็ดเลือดแดงถูกทำลายในผู้ป่วยที่มีภาวะติดเชื้อได้บ่อยกว่าผู้ป่วยที่ไม่มีภาวะติดเชื้อ*

สรุป: *การลดขนาดของคอร์ติโคสตีรอยด์ลงอย่างรวดเร็วและการติดเชื้อเป็นปัจจัยเสี่ยงที่เป็นไปได้ต่อการกลับเป็นซ้ำของโรคโลหิตจางจากเม็ดเลือดแดงถูกทำลายโดยกลไกออโตอิมมูนชนิดไม่ทราบสาเหตุ*