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A Survey of 215 Non-Hemophilic Patients with Inhibitors to Factor VIII

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Key words

Factor VIII inhibitors – Circulating anticoagulants – Acquired antibodies to factor VIII

Summary

Information was obtained by questionnaire about 215 non-hemophilic patients who developed inhibitors against factor VIII (antihemophilic factor). The majority of the patients were over 50 years of age, and approximately equal numbers of males and females were reported. Rheumatoid arthritis was present in 8% of the cases, 7% occurred during pregnancy or the post-partum period, and in several there was an association with allergy to penicillin, asthma, "auto-immune" diseases, or malignancy. In 46% of cases, no underlying disorders were identified. Major bleeding was observed in 87% of patients, and in 22%, death was attributed either directly or indirectly to the presence of the inhibitor.

In 11 of 31 patients receiving no therapy other than supportive transfusions of blood or factor VIII concentrate, the inhibitor disappeared after being present for an average duration of 14 months. Corticosteriods were thought to be effective in abolishing the inhibitor in 22 of 45 patients in whom these were the only drugs administered. Twenty-eight patients received azathioprine as well as corticosteriods; in 19, the inhibitor declined or disappeared during treatment. Finally, 80 patients were treated with cyclophosphamide; in 37 there was a favorable outcome. Inhibitors in children and post-partum patients were more likely to disappear spontaneously or with steroid therapy, whereas those in patients with rheumatoid arthritis or other "autoimmune" disorders required treatment with alkylating agents. However, before any specific therapy can be recommended for this disorder, prospective trials of potential therapeutic agents should be conducted in selected subgroups.

Introduction

There are many unanswered questions with regard to the inhibitors of factor VIII which develop in non-hemophilic patients. Under what circumstances do they appear, do they increase morbidity and mortality, do they disappear spontaneously, are they best treated by steroids or cytotoxic drugs?

Although many anecdotal case reports concerning such inhibitors embellish the literature, there have not been surveys to indicate the importance of this problem, and whether therapeutic measures are justified. We recently asked physicians working in this field to report to us their experiences with such patients, and we now present the results of this survey.

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Material and Methods

Physicians who might have contact with affected patients were drawn from those listed in the manual Comprehensive Care in Hemophilia (1979 Edition), and the membership rolls of the International Society of Haemostasis and Thrombosis. Each physician was sent a questionnaire requesting information on the number of non-hemophilic patients with factor VIII inhibitors seen in the past 10 years. For each patient listed, we requested the method of inhibitor assay used in the diagnosis, the age and sex of the patient, and whether there were any associated disorders or possible predisposing conditions. We asked if the patient experienced major bleeding, such as hemarthroses, melena, intracranial or retroperitoneal bleeding. We enquired about the duration of the inhibitor, and all treatments the patient received during this time. Did the physician think that any particular therapy influenced the course of the illness? Finally, we asked if the patient died, and if the death was directly or indirectly related to the inhibitor. A copy of the questionnaire is reproduced in the Appendix.

Results

Over 200 questionnaires were distributed, and replies were received from 118 physicians, of whom 55 reported that they had not seen any non-hemophilic patients with inhibitors during the past 10 years. The remaining 63 physicians reported on 215 patients. The distribution of patients per physician is shown in Table 1. More than half the patients were seen by physicians who had experience with 8 or more patients.

Methods of Assays

Each physician was asked to identify the method used for assaying the inhibitor. Forty percent used the Bethesda method (1), 22% used the Oxford technique (2), and the remainder used a variety of other methods. Of these, approximately half were previously published methods. Thus, 153 (77.3%) of patients

Table 1 Distribution of patients per physician

	No. of patients	No. of physicians	Percent of all patients
	1	29	13.5
	2	8	7.4
	3	9	12.6
	4	7	13.0
	6	2	5.6
	8	1	3.7
	10	1	4.7
	11	2	10.2
	12	2	11.2
	17	1	7.9
	23	1	10.7
Total	215	63	100.5

1. Anchor Name: her beş hastaden birinde [Agency Turkey sibel.cakan@pitstop.com.tr]

were diagnosed using previously published methods of assay. Respondents also indicated the maximum inhibitor titers recorded for their patients. For purposes of classification, we arbitrarily considered patients to have high titer inhibitors if they had more than 2 Oxford units, 5 Bethesda units, 10 Malmo units or 50 Case Western units of inhibitor.

Age and Sex Distribution

One hundred and eight (52.7%) of the patients were male, and 97 (47.3%) female. The age distribution is shown in Table 2. More than half the patients were older than 50. The small peak at age 21–30 consisted mainly of post-partum patients.

Associated Disorders

The various underlying disorders in these patients are shown in Table 3. In 46.1% of patients no underlying disorder was identified. However, in a total of 18%, rheumatoid arthritis, systemic lupus, or other auto-immune disorders were associated with the development of the inhibitor. In 7.3%, the inhibitors occurred during pregnancy or in the immediate post-partum period. A striking finding was the association of several cases with drug reactions either to penicillin, ampicillin, or phenytoin. A relationship to penicillin reactions has been previously reported (3).

Five cases were reported in association with asthma, three with psoriasis, and two with pemphigus. Multiple transfusions were thought to play a part in 5 other cases. Finally, inhibitors were associated with various malignancies, diabetes, and other diseases in a number of patients. However, the fact that both inhibitor development and these disorders tend to occur in the elderly may indicate a coincidental relationship.

Table 2 Age distribution of affected patients

Age (years)	No. of patients (%)
1–10	6 (3.7)
11–20	7 (4.3)
21–30	13 (8.0)
31–40	5 (3.1)
41–50	14 (8.6)
51–60	28 (17.2)
61–70	40 (24.5)
71–80	39 (23.9)
81–90	12 (7.4)
Total	163 (100.7)

Table 3 Underlying disorders in non-hemophilic patients with factor VIII inhibitors

Disorder	No. of patients (%)
None identified	82 (46.1)
Rheumatoid arthritis	14 (7.9)
Post-partum	13 (7.3)
Malignancy Lymphocytic leukemia and lymphoma (5), solid tumors (lung, colon, kidney)	12 (6.7)
Drug reactions* Penicillin and ampicillin (8), phenytoin (3), chloramphenicol	10 (5.6)
Systemic lupus erythematosus	10 (5.6)
Other auto-immune disorders Temporal arteritis (2), ulcerative colitis, dermatomyositis, myasthenia gravis, polymyositis, Sjögren's syndrome	8 (4.5)
Dermatologic disorders Psoriasis (3), pemphigus (2) exfoliative dermatitis (2), erythema annularis centrifugum	8 (4.5)
Respiratory disorders Asthma (5), sarcoid, respiratory failure	7 (3.9)
Multiple transfusions	5 (2.8)
Other Diabetes (3), Hepatitis (2), Hyperglobulinemia (2), Glomerulonephritis (1), Polycythemia (1)	9 (5.1)

* 2 patients received both penicillin and phenytoin

Morbidity and Mortality

Major bleeding, including hemarthroses, melena, hematuria, intracranial or retroperitoneal hemorrhage, or other bleeding requiring transfusions, was reported in 164 or 87% of the patients for whom this information was available. Of even greater significance was the fact that 40 or 22% died either directly or indirectly as a consequence of having the inhibitor.

Outcome in Relation to Therapy

Thirty-one patients received no therapy other than transfusions of blood or factor VIII to control specific bleeding episodes. Two patients were lost to follow-up, and 8 died after having their inhibitors for a median duration of 12 months (range, 2 weeks to 4 years). Ten patients still have their inhibitors (median duration 36 months (range, 1–156 months). In the remaining 11 patients, the inhibitor spontaneously disappeared after being present for an average of 14 months (median, 10 months; range 1–48 months). The underlying diagnosis in these 11 cases were post-partum (4), asthma (1), ampicillin (1), hyperglobulinemia (1), and no associated diseases (4). Thus, in only two cases were the inhibitors associated with chronic diseases – asthma and hyperglobulinemia. Of interest was the observation that the inhibitor reappeared in one of the post-partum patients when she again became pregnant. Lastly, although a variety of methods were used for assaying the inhibitors, the titers in most of these patients appeared to be low.

Virtually all the remaining patients were treated with steroids, and in 45, this was the only therapy. Doses were quite variable; some investigators gave daily doses of 30–80 mg prednisone; others gave up to 2 mg/Kg daily for 5 days. There was either disappearance or decline in inhibitor titer during therapy in 22 of these patients. The underlying diagnoses in these patients were post-partum (4), multiple transfusion (2), ulcerative colitis, asthma, SLE, and diabetes. In 4 cases no underlying disorder was recognized, and in 8 cases this information was not available. The inhibitor was recorded as still present or the patient died when the diagnosis was rheumatoid arthritis (2), SLE (2), temporal arteritis, polymyositis, postpartum, sarcoid, asthma, respiratory failure, and penicillin reaction. In 3 cases, no underlying disorder was recognized, and in 5 cases, this information was not available.

Twenty-eight patients received azathioprine, generally in combination with prednisone. The usual dose was 100–200 mg per day, for up to 6 weeks. In 19 cases, the inhibitor titer either declined or disappeared during therapy. In three patients the underlying disorder was rheumatoid arthritis, but in 10 others, no underlying disorder was present. Other alkylating agents were given to 8 of these patients along with the azathioprine; in 4 cases the inhibitor disappeared, but it persisted in 4 others.

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Table 4 Outcome in relation to treatment

Treatment	Decline/ disappearance (%)	Persistence died (%)
None	11 (38)	18 (62)
Drug therapy*	78 (58)	56 (42)
Corticosteroids	22 (54)	19 (46)
Cyclophosphamide	37 (57)	28 (43)
Azathioprine	19 (68)	9 (32)
Treated, but outcome not attributed to drug	7	–
Total: All cases	90 (56.5)	74 (43.5)

* 13 patients treated, but lost to follow-up

Note: Discrepancies in totals due to patients receiving more than one drug.

Finally, eighty patients were treated with cyclophosphamide; in almost all cases, in combination with prednisone. The cyclophosphamide was either given in daily oral doses of 100–500 mg for up to 6 weeks, or as a single i. v. bolus of 1–1.5 G, generally along with a dose of AHF concentrate. In 37 of these patients, the inhibitor titer declined or disappeared during treatment. The underlying disorders in these cases were rheumatoid arthritis (6), and one each of 14 other diseases. In 17 of the cases, no underlying disorder was detected. The inhibitor was still present or the patient died in 28 cases; five of these patients had malignancies, and in 15 no underlying disorder was detected. Of interest was the fact that in 7 additional the inhibitor was thought to have disappeared spontaneously, although the patient had received cyclophosphamide. In the remaining 8 patients, information about the outcome was not provided.

The results with the various therapeutic agents are summarized in Table 4. Of interest is the fact that each of the drug therapies gave a better outcome than no treatment. Since most patients received more than one drug, it is not possible to attribute superiority to any particular agent. However, it should be noted that most patients received corticosteriods initially, and if they did not respond, an alkylating agent was added. Thus, the latter agents were generally used in patients with the more resistant inhibitors.

The outcome in relation to treatment was further analyzed in two subgroups of patients – those with rheumatoid arthritis, and those with postpartum inhibitors. The results are shown in Tables 5 and 6. The analysis shows that in no patient with rheumatoid arthritis did the inhibitor decline or disappear without therapy or with prednisone alone, with one possible exception. On the other hand, addition of an alkylating agent was accompanied by disappearance of the inhibitor in 8 of 10 cases. In contrast to this result are findings in patients with post-partum inhibitors. In 8 of 13 patients, the inhibitor either disappeared spontaneously or with corticosteroid therapy alone.

Table 5 Outcome in patients with rheumatoid arthritis

Treatment	Decline disappearance	Persistence death
None	–	1
Drug therapy		
Prednisone	–	2
Cyclophosphamide	2	–
Prednisone + Cyclophosphamide	3	–
Prednisone + Azathioprine	2	1
Prednisone + Cyclophosphamide + Azathioprine	1	1
Treated, but outcome not attributed to Prednisone + Cyclophosphamide	1	–
Total	9	5

The relationship of outcome to inhibitor titer was also examined. All but one of the patients with rheumatoid arthritis had high titer inhibitors (exception was a patient whose inhibitor disappeared during therapy with prednisone and cyclophosphamide). Treatment with prednisone as a single agent was of no apparent benefit in these arthritis patients, but did seem effective in 4 post-partum patients, 3 of whom had high titer inhibitors. Spontaneous disappearance of the inhibitor occurred in 2 post-partum patients with low titer inhibitors; the inhibitor titers in 2 other patients with this outcome were not reported.

Table 6 Outcome in post-partum patients

Treatment	Decline disappearance	Persistence death
None*	4	1
Drug therapy		
Prednisone, ACTH	4	–
Prednisone + Cyclophosphamide	1	1
Azathioprine	1	–
Treated, but outcome not attributed to Prednisone + Cyclophosphamide	1	–
Total	11	2

* One reappeared with next pregnancy

Inhibitors declined or disappeared during drug therapy in 40% of patients with SLE or other autoimmune disorders, in half the patients with skin diseases, but in only one patient with a drug reaction. In four of five untreated patients with drug reactions the inhibitors persisted or the patients died.

Inhibitors in Children

Inhibitors were reported in 9 children between the ages of 5 and 16; there were 2 girls and 7 boys. Two appeared during penicillin or ampicillin therapy, two occurred in the immediate post-operative period, and one was in association with asthma. The inhibitor disappeared spontaneously in 4 patients after an average of 4 months, but persisted in 3 others for more than 3 years despite steroid therapy. The remaining 2 patients were treated with cyclophosphamide; the inhibitor disappeared after 2½ months in one child, and after nine months in the patient with asthma. Thus, in 6 of the 9 children the inhibitor subsided; in 4 with no need for therapeutic interventions other than transfusion.

Discussion

Inhibitors of factor VIII in non-hemophilic patients are rarely encountered in clinical practice. Therefore, it has been difficult to determine how much of a threat they pose to the patient, and whether therapeutic efforts to suppress them are justified. Furthermore, there are anecdotal reports that these anticoagulants may disappear spontaneously, suggesting that exposing the

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patient to potent immunosuppressive and possibly oncogenic drugs may be unwarranted. Finally, there is conflicting evidence concerning the superiority of immunosuppressive agents as compared to corticosteroids. The purpose of this survey was to gain information about the morbidity and mortality associated with these inhibitors, the frequency with which they are associated with other diseases, and whether any of the drugs commonly used therapeutically have any significant effect on the natural course of the inhibitor.

We found that the majority of patients with inhibitors were over 50 years of age, with a second small peak of incidence in women around the time of parturition (Table 2). In approximately half the patients there were no obvious associated diseases, but in 8% an association with rheumatoid arthritis was found, and 6% each were in patients with malignancy, systemic lupus erythematosus, and drug reactions (Table 3).

The development of the inhibitor had serious consequences for the patient; 87% of the patients experienced serious bleeding, and in 40 or 22%, death was attributed directly or indirectly to the presence of the inhibitor.

In 11 of 29 patients (38%), the inhibitor disappeared spontaneously after being present for a median duration of 10 months (range, 1–48 months) (Table 4). These were mainly patients in the post-partum period (4), or without associated disorders (4), and the inhibitors had generally been present in low titer.

Twenty-two of 41 patients had their inhibitors disappear during corticosteroid therapy, 37 of 65 during cyclophosphamide treatment, and 19 of 28 with azathioprine administration. Thus, 58% of patients were thought to have benefited from drug therapy. Further analysis revealed that most post-partum patients improved spontaneously or with steroids alone, whereas patients with rheumatoid arthritis required alkylating agents for a favorable outcome. In children, a favorable outcome occurred without therapy other than transfusions in 4 of 9 cases. In 3 patients the inhibitor persisted despite steroid therapy, and in two patients, subsidence was associated with cyclophosphamide treatment.

This survey sought an answer to the question of whether the disappearance of the inhibitor could be attributed to a specific therapy. Our results indicate that inhibitors disappear relatively infrequently in untreated patients, and generally in those with low titers. The much higher disappearance rate in the treated patients strongly suggests that therapy does accelerate inhibitor disappearance. However, a prospective, controlled study with patients randomly assigned to therapy or no-therapy groups is needed to answer this question.

Finally, it should be pointed out that in contrast to previously published reports which generally emphasize response to a particular therapy (4–8), the present survey provides data on an unselected patient population including those not receiving any treatment. These case records are probably more representative of the clinical course of most patients with this disorder. The data reported should encourage collaborative clinical trials of various therapeutic agents in selected patient subgroups.

Appendix

Questionnaire

1. How many non-hemophilic patients with inhibitors to factor VIII have you encountered during the past 10 years?
2. For each patient, would you furnish the following information:
   A. Method of Inhibitor Assay:
   B. Titer of Inhibitor (maximum titer):
   C. Nature of any underlying disorder or possible predisposing condition:
   D. Age and Sex:
   E. Presence of major bleeding (included are hemarthroses, hematuria, gastrointestinal bleeding, intracranial or retroperitoneal hemorrhage, or other bleeding requiring transfusion):
   F. Were any of the following administered:
      a) Factor VIII concentrate? (Indication?)
      b) Prednisone
      c) Cyclophosphamide
      d) Azathioprine
      e) Other cytotoxic/immunosuppressive
      f) Exchange transfusion or pheresis
      g) Other therapeutic measures
      h) Length of time inhibitor was present – from historical presence to laboratory diagnosis to disappearance or the last examination of the patient.
         (1) During how much of this period was inhibitor titer constant.
         (2) Did inhibitor subside without therapy or did you attribute a particular therapeutic measure to disappearance of inhibitor.
         (3) Did patient die as a consequence of the inhibitor, either directly or indirectly.
3. How many patients with classical hemophilia are known to your Center? Your name and Center:

Thank you.

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