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*Original Contribution*

# RENAL CHANGES IN HAEMOPHILIA A

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## ABSTRACT

Haemophilia A is an X-related inherited disturbance of haemostasis associated with the Factor VIII gene. The aim of our study was to determine the rate, the type and the severity of signs from the urinary tract and their dependence on disturbances in the Factor VIII gene. Twenty-one patients with Haemophilia A, aged 3 to 18, were studied. We used a combination of clinical laboratory investigations and changes in the urinary tract gene defects related to Haemophilia A. During the 5 years of investigation bleeding from the urinary tract was found in 23.8% of patients. The number of patients with haematuria was variable in this period. The duration of macroscopic haematuria was usually short. Urine changes were dynamic during the day. Big clots sometimes caused abdominal and lumbar-sacral pain. Apart from macro-and microscopic haematuria, we found also cases of proteinuria and leukocyturia. The analyses of the gene coding Factor VIII in patients with haemophilia A and haematuria showed five gene defects; renal function was usually preserved in all cases. We observed in all these defects cases of severe clinical form of Haemophilia A.

**Key Words**: Haemophilia A, haematuria, mutation, insertion, inversion

## INTRODUCTION

Haemophilia A is an X-related inherited disturbance of haemostasis. The disease is a result of insufficiency or full absence of functionally active Factor VIII

The gene coding for the synthesis of Factor VIII is situated on the long arm of X-chromosome (X-q28). Its longitude is 186 kb and its coding sequence is situated in 26 exons [1](**Figure 1**).

Clinical manifestation of the disease is quite variable. Usually physician's attention is directed towards obvious and painful clinical signs.

Urinary tract bleeding most often is without history of trauma. It is not long lasting and ceases spontaneously without causing any pain or discomfort. Thus it stays away from the physician's attention.

The aim of our study was to determine the rate, the type and the severity of urinary tract signs, especially haematuria, and its dependence on the disturbances in Factor VIII gene.

## MATERIAL AND METHODS

Twenty-one boys with Haemophilia A, aged 3 to 18, were studied.

In the study period (2000 – 2004) they were admitted to hospital 156 times on the total, with an average admission of 1.5 times per patient yearly.

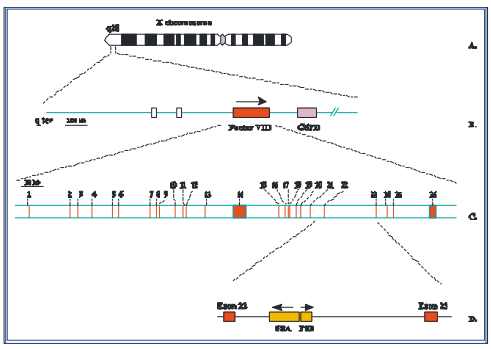

***Figure 1: The gene coding the synthesis of Factor VIII***

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Routine haematological and urinary studies were performed with standard procedures. DNA was isolated from peripheral white cells by the procedure described by Poncy, M. et al. [2]. Southern blot analysis [3] was performed by digestion of genomic DNA with restriction enzyme – Taq I and hybridisation with a partial fVIII cDNA probe coverning exons 14-26. The details about the investigation of molecular characteristics of haemophilia A are presented in our previous reports [4, 5].

## RESULTS AND DISCUSSION

Bleeding from the urinary tract is relatively common in our patients with Haemophilia A during the 5 years of investigation. It is observed in nearly 23.8% of patients. The number of patients with haematuria is variable in these years as not all patients have haematuria each year.

One exception is a 15 year-old patient with haematuria each year.

Haematuria is usually observed in children older than 12 – 13 years. Usually there is no history of preceding trauma.

The duration of macroscopic haematuria is usually short – 2 – 3 days and ceases spontaneously, while microscopic haematuria lasts 5 – 7 days.

Urinary changes are dynamic during the day. Early morning urine is most coloured from blood and later in the day urine becomes lighter.

Big clots sometimes may cause abdominal and lumbar-sacral pain when passing through the urethra. Sometimes the pain is suprapubical most often when there is a clot in the bladder (**Figure 2**).

An interesting finding is that even in untreated patients blood in urine is able to coagulate. Probably this is due to the presence of thromboplastin in urine [6].

Thus we do not use antifibrinolytics, as they can lead to forming of insoluble clots and kidney obstruction. In our practice we refrain from application of Factor VIII at the beginning of haematuria and we wait if the bleeding will not cease spontaneously. Patients are well hydrated orally and if it is required - intravenously during the night. In the next morning 25 IU/kg b.w. Factor VIII is given and this is repeated in 8 – 12 hours. Treatment modality is similar to that of other authors (Lisichkov, 1986; Seremetis, 1997) [7, 8].

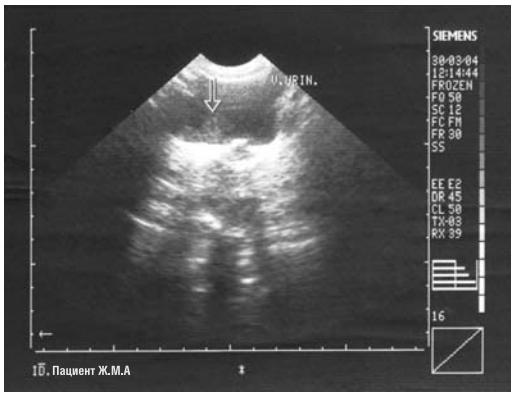


***Figure 2. Ultrasonography showing a clot in the bladder***

Concerning the application of steroids, points of view are contradictory. Some recommend 3 days steroid therapy 1 mg/kg prednisone first day with decrease to 10 mg following day [9, 6]. Other authors do not confirm the efficiency of steroid therapy in patients with Haemophilia A (Rizza, 1997) [10].

Our rate of haematuria in patients with Haemophilia A is lower than that reported by other authors (Stuart et al., 1996; Rizza, 1997) [9, 10].

There are some investigations concerning the long-term effect of haematuria upon kidney function. In a study of Prentice et al. (1997) [11] intravenous pyelography showed changes in kidneys and deviation routes in 38% from investigated patients who had no recent haematuria. They found dilation of pyelon or urether, suggesting flow obstruction in 10% of the investigated patients.

We did not find changes in urinary tract on intravenous urography in our patients.

Sometimes haematuria can be a concomitant manifestation of retroperitoneal bleeding. Probably this results from compression and rupture of small intrarenal vessels especially if vena renalis is compressed. If haematuria is more frequent and if it is accompanied by unusual pain or significant clots, it is necessary to look for liable disease of kidneys or bladder.

Abdominal ultrasound investigation, urine culture and cytology, intravenous urography and/or micturition cystography are proper tests.

Our study was similar to other studies [1, 7, 8, 9, 10, 11]and it shows that the frequency of haematuria decreases during last 5 years. This is probably due to better therapy and home prophylaxis. Possibly reduced

intake of aspirin and aspirin-containing products also plays some role as they damage platelet function.

Haematuria does not cause significant anaemia.

Investigating Factor VIII gene in patients with Haemophilia A and haematuria we found the following gene defects:

- Alu insertion Ex 14 Cd 1224 (**Figure 3, 4 a, b, c**);
- Inv. Int. 22, Prox type 2 (**Figure 5**);
- Ex 3 Cd 90 AAC→ACC Asn→Thr;
- Ex 11 Cd 531 CGC→TGC Arg→Cys;
- Inv. Int. 22, Dyst. Type 1

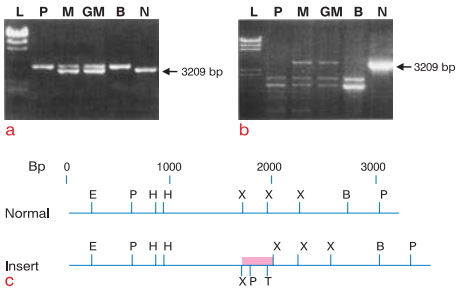


***Figure 3.*** Alu insertion Ex 14 Cd 1224

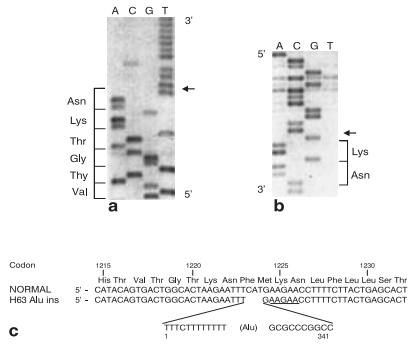


***Figure 4a, b, c.*** Alu insertion Ex 14 Cd 1224

Usually renal function is well preserved. The clinical-genetical comparison shows variable genetical defects, associated with manifestation of haematuria. The common observation is that these gene defects cause severe clinical form of Haemophilia A.

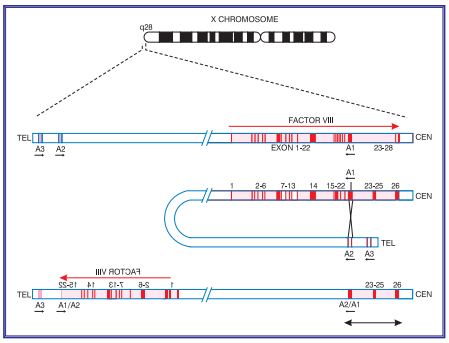


***Figure 5*** - Inv. Int. 22, Prox Type 2

## CONCLUSIONS

1. Haematuria is not a rare sign in Haemophilia A.
2. A variety of gene defects, associated with development of Haemophilia A with haematuria is found.
3. The common observation is that these gene defects cause severe clinical form of Haemophilia A with haematuria.

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