Acquired von Willebrand syndrome as side effect of valproic acid therapy in children is rare

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Summary
To determine the frequency and clinical relevance of acquired von Willebrand syndrome (aVWS) due to antiepileptic therapy by valproic acid, we investigated 50 consecutive children in three neuropediatric institutions. Coagulation factors were determined in local laboratories before and three times after starting therapy with valproic acid. Parameters of von Willebrand factor (VWF) were additionally investigated in a reference laboratory including multimeric analysis. Significant changes in the coagulation system were found concerning fibrinogen (decreased from 287 ± 70 mg/dl to 222 ± 67 mg/dl; p < 0.001) and platelet count. Changes of VWF parameters were also found but no patient developed laboratory defined aVWS. We conclude that the bleeding tendency observed in some children undergoing antiepileptic therapy with valproic acid is not due to aVWS.

In the field of paediatrics, valproic acid is a very important antiepileptic drug for its excellent action in particular in primarily generalized seizures and complex partial epilepsies. In the past, it was considered a drug of first choice because almost no concomitant depressant effects that limit the cognitive development in the patients were observed with its application. Based on initial reports about pronounced hepatotoxicity (12, 26) and pancreatitis impairment, approximately 200 fatal events were published worldwide in connection with liver failure caused by valproate (6). These occurrences almost exclusively affect children under the age of 15 (2). In addition, haemostatic alterations under valproate were reported early on (27).

- Thrombocytopenia (5, 8, 18, 23),
- impairment of the platelet function (9, 17, 23, 24) and
- decrease in coagulable fibrinogen (7, 20)

are known for more than 20 years. Recent analyses indicate an interaction with the FXIII complex (21), and at the same time a decrease in natural inhibitors under valproate (4).

The valproate-induced aVWS was described for the first time in 1990 and 1992 by a working group in Frankfurt (14, 15). The study compared a control group (n = 40) with 30 children receiving valproate and a collective consisting of 43 children with congenital von Willebrand disease (VWD) type 1. The criteria for the diagnosis of aVWS were values lower than 70% of the reference mean value of the
- concentration of VWF: antigen (VWF:Ag by Laurell electrophoresis) or
- ristocetin cofactor (VWF:RCo) (agglutination method) or
- factor VIII activity (FVIII:C) (single phase test).

Based on the similarity of the findings established in the group of patients with congenital VWD for whom the identical diagnosis criteria were used, the overall reported incidence for aVWS under valproate was 67%. Although other working groups were not able to reproduce these alterations involving VWF and FVIII and some authors even excluded alterations involving VWF:Ag (9, 11), the...
recommendations concerning the monitoring of the valproate therapy (13) are based on the frequent occurrence of this side effect. The consequences of these recommendations are extensive, because neuropaediatricians recommend perioperative treatment with DDAVP (13) which is deemed contraindicated by haematologists (14). Haematologists prefer prophylactic substitution of plasma preparations (16) and adhere to this recommendation. Likewise, the significance of valproate-associated aVWS is emphasized (1), and the prophylactic perioperative treatment is recommended. However, both treatment recommendations are so far-reaching and potentially dangerous that the stake in establishing the indication is very high, in particular with respect to the accurate diagnosis of a clinically relevant haemostatic impairment.

**Patients, methods**

A prospective multicenter study was planned to answer the question of how frequent val-

### Tab. 1 Coagulation parameters before and under valproate therapy, mean values, standard deviation (SD), cases (n) and level of statistical significance (p) of change against start values (Wilcoxon test)

<table>
<thead>
<tr>
<th>parameter</th>
<th>before valproate therapy</th>
<th>after start of valproate therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 days</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>mean ± SD</td>
<td>n</td>
</tr>
<tr>
<td>prothrombin time (% Quick)</td>
<td>91.36 ± 5.75</td>
<td>47</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>33.72 ± 7.74</td>
<td>47</td>
</tr>
<tr>
<td>fibrinogen (mg/dl)</td>
<td>287.02 ± 70.15</td>
<td>47</td>
</tr>
<tr>
<td>FVIII : C (%)</td>
<td>132.68 ± 43.00</td>
<td>44</td>
</tr>
<tr>
<td>VWF : RCo (%)</td>
<td>89.36 ± 23.31</td>
<td>44</td>
</tr>
<tr>
<td>VWF : Ag (%)</td>
<td>111.91 ± 39.98</td>
<td>46</td>
</tr>
<tr>
<td>VWF : CB (%)</td>
<td>119.28 ± 52.93</td>
<td>46</td>
</tr>
<tr>
<td>VWF : CB/VWF : Ag (%/%)</td>
<td>1.06 ± 0.22</td>
<td>46</td>
</tr>
<tr>
<td>bleeding time (min)</td>
<td>5.23 ± 1.79</td>
<td>36</td>
</tr>
</tbody>
</table>

aPTT: activated partial thromboplastin time; FVIII : C: factor VIII activity; VWF : RCo: ristocetin cofactor; VWF : Ag: von Willebrand factor antigen; VWF : CB: collagen binding activity of VWF
prote-associated clinically relevant aVWS occurs in children. Fifty consecutive patients from three neuropaediatric centers with epileptological outpatient clinic (Children’s Hospitals of Braunschweig, Hannover auf der Bult, Hamburg-Eppendorf) were prospectively examined during their adjustment phase to valproate. Blood samples were collected prior to therapy start, after one week, two and three months and six or more months of valproate therapy. Standardized coagulation tests including PT, aPTT and fibrinogen (Clauss) were prescribed in addition to the common, relatively thorough routine examinations conducted at the respective outpatient clinics (hepatic, renal and pancreatic function tests, lactate, haemogram, valproate levels). The bleeding time (Ivy, modified according to Mielke), FVIII:C and VWF:RCO were measured at the laboratory of the responsible clinical center prior to starting treatment and at the end of the study. VWF:Ag and VWF:collagen binding activity (VWF:CB) were measured by the reference laboratory (U. B.) at the same time the blood samples were collected, and the multimeric analysis was conducted there at the beginning and end of the study. The examinations were conducted in agreement with the families following in-depth consultation; the Ethics Committee of the Chamber of Physicians of Lower Saxony issued a positive vote for the project.

Results

Of the 50 patients enrolled in the study, 10 could not be included in the evaluation due to missing data sets. The remaining 40 children (22 boys, 18 girls) had complete data sets and were included in the evaluation. The examined group included infants as well as younger and older school-aged children (Fig. 1). All of them were treated with valproic acid for the first time. 21 patients received additional antiepileptic medication. During the therapy adjustment phase, the results of the global tests prothrombin time (PT) and activated partial thromboplastin time (aPTT) did not reveal any alterations with the exception of prolonged aPTT intervals in a few cases (Fig. 1). The fibrinogen levels significantly decreased during the course of the therapy and reached pathological concentrations in 9 of 40 children (Fig. 2a).

The bleeding time revealed a significant prolongation after six months of antiepileptic therapy; 6 of 40 children had a slightly to moderately prolonged bleeding time (Fig. 3). Children with prolonged bleeding time were thoroughly examined with respect to hemorrhagic diathesis. In repeat controls, regular bleeding times were found three times and reduced aggregation to collagen and ADP was found twice. In one child with repeatedly measured prolonged bleeding time (10–12 min), we were unable to identify the corresponding cause.

The examinations concerning VWF/FVIII revealed different influences of the drug adjustment on the measured values. No significant alterations were determined for FVIII:C and VWF:RCO (Tab. 1); none of the values dropped below the regular range in any of the subjects. In contrast, VWF:Ag actually showed a statistically significant decrease over the course of the examination, while none of the patients in the examined collective dropped below the regular range (Fig. 4). After all, 7 of 40 children had elevated values before starting therapy, VWF:CB was measured by means of ELISA, the results were indicated as percentage of the regular value. The measured results were provided as ratio of VWF:CB and VWG:Ag; the regular range is 0.8–2.0. A significant increase of VWF:CB relative to the VWF:Ag was observed starting as early as in the first week of the therapy adjustment period (Fig. 4). Figure 2c illustrates the correlation between the individual measurements compared to the regular values. It reveals that only two individual values with reduced VWF:CB are found at the start of the valproate adjustment phase.

Altogether, we observed a relative decrease in the VWF:Ag concentration with increasing function measured by the VWF:CB. The lower limit of the regular value was not exceeded continuously in any of the patients.

Discussion

The question whether antiepileptic treatment with valproate causes a clinically relevant im-

**Fig. 3** Bleeding time (Ivy) in minutes before and after six months valproic acid (normal < 9.5 min)

**Fig. 4** Change of VWF:Ag concentration (●) in percent of the individual start value (●), after one week (▲), three (■) and six months (×)

●: absolute value (%); ◆: 100% of start value;
Impairment of haemostasis is very significant for affected patients. After all, the current recommendations include the perioperative treatment of children with valproate-associated aVWS with VWF containing FVIII concentrate, because DDAVP can promote seizures in children with epilepsy. The current data concerning the incidence of this drug-induced complication is based on a retrospective analysis of 30 children (14). It compared the laboratory parameters of VWF with results of a control collective not described in detail and a group of children with congenital type 1 VWD. Based on the fact that the deviations of the values in the group of Valproate-treated children corresponded to the ones of children with congenital VWD, it was concluded that two of the three children acquired mild type 1 VWS. VWF:Ag below 70%, measured by EIA, in combination with normal VWF:multimers allowed the confirmation of the diagnosis in 87% of examined patients. In a smaller prospective study (3), type 1 aVWS was diagnosed in 2 of 20 children after six months of Valproate therapy, a significant decrease from 105 to 85% of the VWF:Ag concentration was reported and a significant increase of the VWF:CB observed. The same working group later published a prospective study (4) which showed an increase in VWF function, as measured by increasing VWF:CB and decreasing activities of the physiological inhibitors antithrombin and protein C in addition to decreasing procoagulation factors (fibrinogen, VWF:Ag) during the course of the valproate therapy. An additional retrospective study, published as abstract (28) shows decreased values in 76 of 131 valproate-treated children and confirms the data published by Kreuz et al. (14). A Turkish working group (25) also diagnosed valproate-associated aVWS in 6 of 29 children.

However, clear criteria for the diagnosis of aVWS is usually missing. Several discussion papers were published during the past few years concerning the issues associated with the definition of the type 1 VWD diagnosis (22) and the dependence on the individual blood group (10, 19). The presented study supplies data concerning altered laboratory findings during the adjustment phase to valproate. The diagnosis of VWD is established or excluded based on the regularly conducted laboratory tests by a reference laboratory during the complete duration of the study. In the present paper, the lower limit of normal was assumed to be 50% (22); this figure refers to the regular values established by the laboratory based on measurements conducted in more than 800 normal individuals. The diagnosis of the type 1 aVWS was made dependent on repeated measurements of decreased concentrations and a clinically relevant bleeding tendency. None of the 40 examined children met these criteria. Although the bleeding time reached the pathological range in six cases, none of the children displayed a pathologically decreased value for VWF:Ag. Although a significant decrease of mean VWF:Ag was determined, this appears to be partly associated with significantly elevated values at the start of the study suggesting an acute phase reaction by stress. No correlation of VWF:Ag concentration with valproate levels was seen (Fig. 6), while the correlation of fibrinogen with the valproate level definitely suggests a pharmacological connection. Likewise, VWF:CB measured relative to the VWF:Ag also showed a significant increase (Fig. 5); this was interpreted as improved function of the von Willebrand factor relative to the concentration, i.e. another argument against the clinical relevance of decreasing VWF:Ag concentrations.
Conclusion

In children, treatment with valproic acid frequently results in alterations of the coagulation system. Most common are hypo-fibrinogenemia (decreased from 287±70 mg/dl to 222±67 mg/dl; p < 0.001) and/or thrombocytopenia. In the study presented here, the minor alterations in VWF parameters and FVIII do not justify the diagnosis of aVWS suggesting that aVWS is a very rare event under valproate therapy. The bleeding tendency reported in some children treated with valproic acid cannot be allocated to aVWS.

References