Therapy refractory menorrhagia as first manifestation of Hermansky-Pudlak syndrome

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Summary
Introduction: Oculocutaneous albinism (OCA) in combination with a platelet function defect caused by a disturbed release reaction from platelet δ-granules (storage pool defect – SPD) is typical for the autosomal recessive inherited Hermansky-Pudlak syndrome (HPS).

Case report: A girl (age: 13 years) with OCA was hospitalized with transfusion-requiring menorrhagia. The suspicion of HPS was confirmed by results of lumi-aggregometry. Suspecting a disorder in primary haemostasis treatment with tranexamic acid (10 mg/kg body weight every 8 h i. v.), desmopressin (0.3 μg/kg body weight every 8 to 12 h) and hormonal therapy (norethisterone) was started but the menorrhagia persisted. Clinical response was finally achieved by a single injection of 100 μg/kg body weight recombinant factor VIIa (rFVIIa). Conclusion: The diagnosis of HPS should be suspected in patients with OCA and bleeding symptoms and is confirmed by the proof of SPD. In case of absent clinical response to desmopressin the application of rFVIIa should be considered. Hormones and antifibrinolytics are useful options in the treatment of extensive menorrhagia.

Schlüsselwörter
Hermansky-Pudlak-Syndrom, Menorrhagie, Desmopressin, rFVIIa

Zusammenfassung

A girl with albinism

A 13 years old female patient with oculocutaneous albinism was hospitalized with transfusion-requiring menorrhagia occurring at time of menarche. The bleeding already persisted for 14 days. At time of admission she showed severe anaemia with a haemoglobin concentration of 5.5 g/dl and a haematocrit of 0.15. She received one transfusion unit of erythrocytes and the hormonal therapy with norethisterone was started.

Due to the typical phenotype a disorder of primary haemostasis was suspected, especially a platelet function defect. Antifibrinolytic therapy (tranexamic acid i.v. at 12 mg/kg 3×/d) was started in combination with desmopressin i. v. at 0.3 μg/kg every 8 to 12 h (5 doses in total) (►Fig. 1). The desmopressin-induced normalization of the prolonged collagen/epinephrine PFA 100® closure time did not lead to a clinical response which finally was achieved by a
A single bolus injection of 100 μg/kg recombinant factor VIIa (rFVIIa, NovoSeven®). The transfusion of a total of eight erythrocyte concentrates was necessary.

The suspected diagnosis of Hermansky-Pudlak syndrome was confirmed by the results of platelet function diagnostics which showed a markedly decreased ATP-release in response to thrombin and collagen confirming the platelet δ-storage pool defect (Fig. 2). Platelet flow cytometry confirmed the δ-storage pool defect showing a reduced platelet expression of CD 63 by activation with TRAP. Platelet aggregation in whole blood induced by ADP (final concentration: 20 μmol/l), arachidonic acid (0.5 mmol/l) and collagen (1.0 μg/ml) was slightly diminished.

The desmopressin test which was performed about six weeks after the acute bleeding showed a normalization of the prolonged collagen/epinephrine PFA closure time and an increase of von Willebrand factor antigen and factor VIII activity (Tab. 1). The girl is still treated with a progesterone derivative. The additional application of tranexamic acid, given two days before menstruation until two days after cessation of bleeding, has prevented any further menorrhagia.

Family anamnesis

One of the three siblings of our patient also suffers from oculocutaneous albinism and a δ-storage pool disorder. The mild bleeding symptoms of this sister are characterized by skin bleeding tendency. At the age of 11 years she has not had her menarche yet. The other two younger siblings and the consanguine parents (cousins) neither show an oculocutaneous albinism nor any bleeding tendency. The platelet function diagnostics in these two children and the father is planned. In the mother a δ-storage pool disorder was excluded.

Discussion, conclusion

The typical phenotype of oculocutaneous albinism in combination with bleeding symptoms such as menorrhagia allows the suspicion of a Hermansky-Pudlak syndrome (4, 5). Platelet function testing such as flow cytometry or lumi-aggregometry typically shows the patterns of the δ-storage pool disorder. The diagnosis should be proved by genetic analysis (3, 8, 10).

Eight mutations (HPS1 to HPS8) are known leading to the clinical manifestation of HPS. These subtypes are associated with a different clinical occurrence of HPS (3, 6, 7, 10). Therefore, it is important to perform the molecular genetic analysis to draw conclusions on therapy and even prognosis (9, 10). In our patient the genetic defect could not be found yet because none of the known mutations in the HPS gene are present. The parents are cousins which confirms the autosomal recessive inheritance of the disease.

The differential diagnosis of a Chediak-Higashi syndrome, which is characterized by a variable degree of oculocutaneous albinism, a δ-storage pool disorder and es-

<table>
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<td>VWF : CB (%)</td>
<td>60–130</td>
<td>116</td>
<td>&gt;130</td>
</tr>
<tr>
<td>FVIII : C (%)</td>
<td>50–150</td>
<td>133</td>
<td>235</td>
</tr>
</tbody>
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Tab. 1 Desmopressin testing six weeks after transfusion-requiring menorrhagia
particularly a severe immunological defect (5, 7, 9), is unlikely for two reasons:
● the absence of giant granules in leukocytes and
● the absence of severe infections in the history of both affected siblings.

The use of desmopressin in the management of some inherited platelet disorders including δ-storage pool disorders has been well established despite the lack of clinical trials (1). However, the laboratory and clinical response to desmopressin seems to be individually different in HPS patients (2, 11–13). Our patient showed a laboratory response in the desmopressin test but without clinical success regarding cessation of bleeding. Zatik et al. described a young woman who despite of a prophylactic application of desmopressin prior to delivery suffered from a transfusion-requiring bleeding after the first delivery. The same procedure was successful in the second delivery (13). Cordova et al. investigated 19 Puerto Rican children and detected that the presence of the HPS1 gene mutation seems to result in a poor response to desmopressin (2). Wjermans et al. found a normalization of the bleeding time in two of three patients with HPS after desmopressin infusion (12). Wiegand et al. reported on a one-year old boy with HPS who underwent an adenotomy without bleeding complications after application of desmopressin (11).

The literature as well as our case report suggest that an inter- and intraindividual response to desmopressin in patients with HPS may exist.

In conclusion, the phenotype of oculocutaneous albinism in combination with bleeding symptoms is typical for the diagnosis of HPS which must be confirmed by
● platelet function diagnostics and
● genetic analysis.

The laboratory response to desmopressin in HPS patients should be tested before the first therapeutical use in case of bleedings or invasive procedures. However, as it was shown in the case described a satisfactory laboratory response does only partially predict the clinical effect of desmopressin application.

In case of an absent clinical desmopressin effect the administration of rFVIIa should be considered.

Hormonal substitution and antifibrinolytic agents are useful options in the treatment of extensive menorrhagia.

References