Considerations on port-wine stains and their laser treatment
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Chapter 2

Hereditary port-wine stains: do they exist?

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Abstract

Patients with a port-wine stain applying for laser treatment often mentioned to have a member in the family with a similar birthmark. Of 280 consecutive new patients with a port-wine stain 55 mentioned to have relatives with the same anomaly. Family tendency (19.6%) for vascular malformations in our group was significantly higher than mentioned by others. Pedigrees were made of 32 families with two or more affected members, including probands. We present 9 representative pedigrees of families with three or more members affected by PWS. In these families no clear mode of inheritance can be discerned. Genetic linkage studies identified causative gene defects in certain venous malformations and Rendu-Osler-Weber disease. Knowledge of new theories on angiogenesis and molecular genetics has to be linked to our patients with familial PWS.

Keywords: Port-wine stain; Family tendency; Genetics; Vascular malformations.
Introduction

Vascular birthmarks including stork bites, salmon patches and PWS are frequently found in the newborn (1,2). Osburn et al. mention 53% of 830 and Tan quotes 27% of 1000 newborns with stork bites and salmon patches (2,3). The incidence of PWS is stated as 0.3%-0.6% (1,2).

In several syndromal conditions a combination with vascular anomalies is mentioned (4). Unfortunately, because the distinction between hemangiomas and vascular malformations as proposed by Mulliken et al. is not consistently used, interpretation of data from literature is difficult (5). Burns and Mulliken reclassified syndromes and vascular anomalies and made the subdivision “macular stains” next to hemangiomas and vascular malformations (6). Macular stains (stork bite, salmon patch) are thought to be transient lesions, occurring in the glabellar region, eyelids, nape of the neck and alae nasi. They published a list of syndromal associations with macular stains, hemangiomas and vascular anomalies. In hemangiomas a female predilection was found, while in malformations males and females were equally affected (7).

In spite of the relative frequent occurrence of PWS, only a few reports on familial aggregation are found in literature (8,9,10,11,12). Some authors suggest a positive family history of 10% of either PWS, nape and neck lesions or strawberry hemangiomas (13,14). A family with evidence of autosomal dominant inheritance in Klippel-Trenaunay syndrome was identified and in families with this syndrome different members with birthmarks were found (15,16). Blei et al. identified and presented 6 pedigrees of kindred’s in which multiple members were affected by hemangiomas, some in combination with vascular malformations (17). Leblanc et al. mention a relation between vascular malformations in the skin and cerebrum in two families (18). Glomangiomas, which clinically resemble venous malformations are sometimes hereditary (19).

As part of an investigation on efficacy of the flash-lamp-pumped pulsed-dye laser for treatment of PWS we included in the patients medical history inquiries about vascular malformations in relatives (20). Familial occurrence of PWS in these series of these patients was further studied by designing pedigrees. Our goal was to find out about possible familial aggregation. This could be the first step in the search for genetic mechanisms responsible for the development of PWS.

Methods

All patients applied for laser treatment at the division of Plastic and Reconstructive Surgery of the Academic Medical Center, Amsterdam. At first consultation we inquired if these patients had other relatives affected by PWS or other vascular malformations. A PWS is a capillary vascular malformation. These vascular anomalies are by definition present at birth, grow commensurate with the child, and do not show progression or regression (5). Some relatives were described as having hemangiomas which were diagnosed by medical history and time course of the complaints (hemangiomas are vascular lesions that grow after birth or sometimes are present from birth and show...
regression in infancy (5)). The presence of hemangiomas was not recorded in our patients. After finishing treatment we contacted again those patients who mentioned a positive family history for PWS during their first visit for validation of the family history. Then a thorough medical history of all family members over three generations was obtained. Localization of the vascular malformation was noted and pedigrees were constructed of all families with two (including proband) or more affected members.

Results

In a four years period (1992-1996) we saw 280 consecutive new patients with a portwine stain (PWS). Of the 280 patients 55 mentioned to have one or more family members with a vascular malformation. Three times two different members of the same family applied for treatment. Unfortunately, not all patients with a positive family history could be contacted again: 20 patients were lost to follow-up. We were able to draw 32 pedigrees over three generations. Analysis of these 32 pedigrees showed 85 individuals with a vascular malformation, among a total number of 1460 family members. The male (n=23) to female (n=62) ratio of PWS was 1:2.7 in this group. In the group where extensive pedigrees could be drawn, probands presented themselves 25 times with a PWS in the face, two times with their stain on a leg, three times on the arm, one on the trunk, one on the lateral side of the body. Their relatives had PWS localized in the face (22), arm (8), trunk (6), leg (7), or multiple localization's (10) (table 1). In two cases near family members presented themselves with facial venous malformations. Of the 9 families with at least three affected members representative pedigrees with accompanying clinical descriptions are presented below.

<table>
<thead>
<tr>
<th>Location in proband (n)</th>
<th>Location in family (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>Face: 20 Leg: 5 Arm: 6 Trunk: 5</td>
</tr>
<tr>
<td>Leg</td>
<td>Face: - Leg: - Arm: 1 Trunk:1</td>
</tr>
<tr>
<td>Arm</td>
<td>Face: 1 Leg: 1 Arm: 1 Trunk:1</td>
</tr>
<tr>
<td>Trunk</td>
<td>Face: - Leg: 1 Arm: - Trunk: - Multiple locations: 10</td>
</tr>
<tr>
<td>Lateral side body</td>
<td>Face: 1</td>
</tr>
</tbody>
</table>

Table 1  Relation of location of port-wine stain in proband to location of port-wine stains in relatives.
Legends to pedigrees

Fig 1: In this family (NL 060) mother (II-1) has several PWS, on the inside of her hand, left arm, foot and neck. She has two affected daughters: (III-1) having a PWS on the trunk, (III-2) on the upper-leg, and one unaffected son. Two of her brothers and three of her sisters have PWS: (II-2) on both upper extremities and neck, (II-3) on left leg and right arm, (II-4) on head and back, (II-5) multiple small PWS all over her body, (II-10) on one arm and on her face. Grandmother (I-1) has multiple small patches on her trunk. Girl (III-5) has small stains in her neck, on both legs and on her trunk, boy (III-7) has a small spot in the face. Unaffected family members never had affected children.

Fig 2: This family (NL 086) has affected members in the maternal and paternal branches of the pedigree. Proband (V-5) has a large facial PWS as has (V-4), the son of his father’s brother. Grandfather from fathers’ side (III-2) has multiple stains all over his body. From the side of the probands mother (III-8) has a stain in the neck.

Fig 3: Several affected members are detected in this family (NL 204). Proband (III-56) has a large facial PWS, niece (III-18) has a PWS on her leg, niece (III-42) has a small stain on her face, niece (III-54) has a venous malformation of her face while her brother (III-55) has a huge PWS on his arm.

Fig 4: Proband (III-8) in family (NL 223) has a PWS in his face. His aunt (II-1) and grandfather (I-1) from father’s side have a PWS on neck and face, respectively. His niece (V-3) has a stain on arm and upper leg. Father of the proband has a pigmented stain on his thigh.

Fig 5: This female (III-1) in family (NL 190) presented herself with a facial PWS. Two daughters of her uncle from mother’s side do have a PWS on their hand (III-5) and back (III-6).

Fig 6: Proband (III-6) in family (NL 156) has a facial PWS with neurological symptoms. Her father (II-5) has a stain on his trunk. Her fathers’ sister (II-4) has a PWS on her neck.

Fig 7: This boy (III-1) in family (NL 237) has a nephew (III-5) and niece (III-4) with an capillary anomaly on head and ear respectively.

Fig 8: In family (NL 110) three generations each have an affected female. Proband (III-1) has a facial PWS, her mother (II-1) has a small stain on her neck and her grandmother (I-1) has a PWS on the left side of the face.

Fig 9: These data resemble data in the pedigree of Fig. 8. Proband (III-1) has a large PWS on her arm, her mother (II-1) has a stain on her foot, as has her grandmother.
In one family (NL 204) a patient with a PWS mentioned a family member with a venous malformation. Another family (NL 084) was identified (not reported in this series), in which a brother of the proband with a PWS had a venous malformation in the floor of his mouth.

**Discussion**

Our careful patient inquiry showed familial tendencies for vascular malformations in 55 among 280 new patients (19.6%). This is significantly more than generally suggested (0.3% - 0.6% incidence) and even more than twice the incidence mentioned by Mills et al. (1,2,14). These last authors mentioned a positive family history on PWS in 22 of 283 patients (8%).

Relatively many parents of young children applied for treatment. When a child with a PWS is born, one tends to recall other affected family more easily. This may explain our higher percentage of positive family histories.

In some of our families autosomal dominant segregation was obviously (family NL 60) suggestive. In other pedigrees the mode of inheritance was less clear.

Our protocol did not include systematic questions regarding other (non) pigmented lesions, nevi anemic, or hemi-hypertrophy, although these lesions were mentioned to occur in some relatives of patients in our group. Also other authors mentioned such lesions which often seem to be related to PWS (14). We identified a pedigree (NL 223) where one member has a pigmented nevus (Fig 4) and another family (NL 35) where a family member has a nevus anemicus. However we believe that these data are not conclusive for a relation between (non) pigmented and vascular lesions.

Nevus flammeus or PWS has been shown to be derived from a progressive ectasia of the superficial vascular plexus of the skin. The cause of this progressive vascular dilatation remains unclear. Rosen and Smoller documented a marked decrease in nerves associated with these abnormal vessels compared to normal (21). They mentioned lack of sympathetic nerves to regulate blood flow as the cause of the progressive vascular ectasia. Earlier immunofluorescence studies of fibronectin, factor VIII and collagenous basement membrane-type IV collagen did not show abnormalities in the vessel wall (22). In ultrastructural observations of PWS various alterations of the intervascular connective tissue were found (23). However, recent histopathologic investigations did not reveal new insights on the etiology of vascular malformations.

On the other hand the genetic basis of several diseases associated with vascular malformations have been elucidated in the past few years. In a mini review, Folkman et al. went into the molecular basis of blood vessel formation (24). Endoglin, a TGF-beta binding protein for endothelial cells, has been shown to be the gene for hereditary hemorrhagic teleangiectasia (Rendu-Osler-Weber disease) (25). In a second form active receptorlike kinase -1 gene is mutated (26,27). A missense mutation resulting in an arginine-to tryptophan substitution at position 849 in the kinase domain of receptor tyrosine kinase, TIE 2 segregates with dominantly inherited venous malformations (28,29). These authors conclude that the TIE 2 signaling pathway is critical in the endothelial-smooth muscle cell interaction in venous morphogenesis, leading to defects in the differentiation of mesenchymal cells into pericytes and smooth muscle cells, and
to insufficient matrix deposition. Of course, much attention is paid to inherited intracerebral vascular malformations where linkage was shown to chromosome 7q (30).

Conclusion

The understanding of the etiology of vascular malformations is changing. Genetic linkage has been successful in identifying specific genetic defects. Detection of families affected by vascular malformations (in casu PWS) is the first step towards a molecular analysis. Next step will be to go for DNA material in search for candidate genes. However therapeutic consequences are unlikely to be expected in the near future.

References


Figure 5

NL190

Figure 6

NL156
Figure 7

NL237

I

II

III

1

4

5

2

Figure 8

NL110

I

II

III

1

1

1

1
Figure 9

NL136

Legend to figures

- ■  ● Male, female affected; ID number
- 1  8
- 2  ○ Male, female unaffected, number of persons
- 1 Generation indicator
- ▶ Index patient
- NL01 Family ID