Improvement of disfiguring skin conditions by laser therapy
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HYPERTROPHY IN PORT-WINE STAINS: PREVALENCE AND PATIENT CHARACTERISTICS IN A LARGE PATIENT COHORT

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ABSTRACT

Background: Port-wine stains (PWS) may thicken and darken with age. Little is still known on pathogenesis and epidemiology of hypertrophy in PWS due to the lack of large studies.

Objective: To assess prevalence and characteristics of patients with hypertrophic PWS.

Methods: Medical records and clinical photographs of all patients with PWS visiting our outpatient clinic between 2005 and 2009 were examined to identify hypertrophy. Patients were sent questionnaires regarding their hypertrophic PWS.

Results: 335 patients (0-81 years; 69% female) with PWS were included. Hypertrophy was found in 68 patients (20%; 32 male, 36 female) and was classified as thickened (5.1%), nodular (8.1%), or both (7.2%). Color of hypertrophic PWS was mainly red (50%) or purple (44%). Patients with hypertrophy in their PWS were mostly (68%) over 40 years, and rarely (7%) under the age of 20. Above the age of 50, 71% of all patients had hypertrophy in their PWS. Median age of onset of PWS hypertrophy was 31 years (12 years for thickened, 39 years for nodular hypertrophy).

Limitations: This was a retrospective study in a selected population.

Conclusion: Hypertrophy is an important feature in the development of PWS which affects a majority of patients above 50 years of age. Color of the PWS is associated with hypertrophy, whereas location and size of the lesion appear not to be related. More attention should be drawn to therapy and prevention of hypertrophic PWS. Also, diffuse thickening and nodules should be differentiated, as a different age of onset indicates different pathomechanisms.
INTRODUCTION

Port-wine stains (PWS) are congenital capillary malformations seen in approximately 0.3% of newborns. They are frequently located on the face and neck, but can present anywhere on the body. While generally flat and pink in infancy, PWS may thicken and darken in color during adult life due to progressive vascular ectasia.

Treatment of PWS has improved since the introduction of the pulsed dye laser (PDL) in the 1980’s. Despite adjustments in technique over the years, the results of laser therapy are unsatisfactory in 20% of patients. PWS often lighten in color with laser therapy, but rarely disappear completely. Blue-purple, hypertrophic PWS in particular do not respond well to treatment with the pulsed-dye laser.

Little is known about development of hypertrophy in PWS. Finley et al. reported hypertrophy in 2 of 500 patients with PWS, referring to a cobblestone pattern; in 5 additional patients, they observed tumors consisting of proliferating vessels. Geronemus and Ashinoff determined that nearly two-thirds of patients with PWS develop nodules and hypertrophy by the fifth decade of life.

Dermatology textbooks cite two studies. Mills et al. reported 31 (10%) cases of PWS with hypertrophy in a demographic study of 283 patients. Klapman et al. described the prevalence (40%) and characteristics of thickening and nodules in 173 PWS patients. The peak age of onset of hypertrophy was between of 20-39 years and the prevalence of nodules increased with age.

Port-wine stains are known to have a negative influence on psychological well-being. The aim of our study was to assess the prevalence and characteristics of patients with hypertrophic PWS.

METHODS

Patients

This study cohort comprised all patients with a PWS who consulted the Netherlands Institute for Pigment Disorders between September 2005 and March 2009. Patients were eligible for inclusion if they had a PWS recorded in their medical file and digital photographs. Patients with Klippel-Trenaunay syndrome were not present in our database. Records were reviewed for gender, age, hypertrophy, color of the PWS, location on the body, and details of previous treatments. Hypertrophy was identified by a physician and classified as either nodular, describing papules and nodules arising in the PWS, or as diffuse thickened, describing both larger plaques and deeper thickening of underlying structures (Figure 1). Characteristics of patients with flat PWS were compared to those of patients with hypertrophic PWS.

A questionnaire was sent to patients who appeared to have a hypertrophic PWS with questions regarding color change, thickening and/or nodules, age at onset of these changes, the main reasons for initiation of laser therapy, and the impact on their daily life. Adult patients were asked to complete and return the questionnaire. Patients under 18 years of age completed the questionnaire with the help of their parents. Similar questionnaires were sent to an age-matched control group with flat PWS.
Statistical analysis
We chose to analyze all questionnaires and entered them into a Microsoft Office Excel 2003 database together with the characteristics of every patient. Statistical analysis was performed using SPSS software version 16.0 (Statistical Package for the Social Sciences. Chicago, IL, U.S.A. SPSS Inc.). Continuous variables were presented as medians with interquartile ranges. The proportions were presented as percentages with a 95% confidence interval (CI). We used multivariate logistic regression models to quantify the risk factors for hypertrophic PWS. Potential confounding factors were evaluated based on a significant outcome (95% CI) in the univariate regression analysis.

RESULTS
Patient characteristics
We identified 342 patients with PWS of which 7 were excluded due to absence of digital photographs in the file. The remaining 335 patients were included and analyzed. The majority was female (231 patients, 69%). The median age at the time of database screening was 22 (0-81 years, interquartile range 14-41 years). The most common PWS location was the face (68%) with the majority on the cheeks. The color of the PWS was usually red (49%). Sixty-eight of 335 patients (20%; 95% CI=16.0-24.6%) had hypertrophic PWS (Table 1). There was an equal male-female ratio (32 male, 36 female). The median age of this subgroup at the time of database screening was 50 years (12-81 years, interquartile range 32-57 years).

The most common location for hypertrophic PWS was the face (79%) with hypertrophy involving the cheeks in the majority of cases. There were less hypertrophic PWS on the extremities (10%). The pattern of distribution on the face was similar between hypertrophic and all PWS. The color of the lesion was often red (50%), and few were pink. Hypertrophy was classified as thickened (25%), nodular (40%), or both thickened and nodular (35%). Both types of hypertrophy were present in equal proportions on the body and on the face (Table 1).

In the univariate regression analyses, size of the PWS and location were hardly or not at all significantly associated with hypertrophy. Older age was highly associated with hypertrophic PWS (OR=1.09 per year; 95% CI=1.065-1.108). In the multivariate regression analysis that adjusted for other significant risk factors such as sex, color of the PWS and location on the face, neck or upper extremities, age remained associated with a higher risk of hypertrophic PWS (OR=1.1 per year; 95% CI=1.072-1.124).

Dividing all PWS according to age we noticed that hypertrophic PWS were rarely seen in patients under the age of 20 (7%), and mostly above the age of 40 years (68%) (Figure 2). Only 48 (14%) of the 335 patients were over 50 years of age. Thirty-four (71%; 95% CI=56.9-82.3%) of these 48 patients had PWS hypertrophy. We found diffuse thickening of the PWS in all age groups, whereas nodular and combined (diffuse and nodular) hypertrophy was mostly seen in patients between 41-60 years of age (Figure 3).
Questionnaires
Sixty-three of 68 patients with hypertrophic PWS returned completed questionnaires (93% response). Control patients (63) with flat PWS were also sent a questionnaire, of which 75% were returned. Matching by age was not possible as there were hardly any elderly patients with a flat PWS.

The median age at onset of hypertrophy in the PWS was reported to be 31 (0-65) years. The median age at onset of nodules and diffuse thickening was 39 (11-50) and 12 (0-65) years respectively. Forty-four patients answered this question.

The main reasons given for starting laser treatment in flat PWS patients were the color (72%) and the impossibility of camouflaging the PWS (53%). The main reasons for starting laser treatment in patients with hypertrophic PWS were also color and inability

Figure 1. Examples of hypertrophy in port-wine stains (PWS). A. diffuse thickened PWS on the back of the head of an elderly male patient. B. diffuse thickened PWS (thickening of underlying structures) on the upper lip of a child. C. nodular hypertrophy in a PWS on the upper left leg of a female patient. D. nodular hypertrophy in a PWS on the left cheek of a male patient.
to camouflage the lesion (66% and 35% respectively), but hypertrophy was also of importance; 27% of patients reported PWS thickening and 31% reported nodules as a reason to start laser treatment. Thirty percent of patients with hypertrophic PWS identified irritation of clothing and bleeding of the hypertrophic facial PWS when shaving or combing hair as reasons for seeking laser treatment. Thirty-one percent of patients with flat PWS reported use of cosmetic camouflage on a daily basis, with moderate to good results. Of patients with hypertrophic PWS, only 11% applied camouflage therapy on a daily basis, also with moderate to good results. Among flat PWS patients, 31% experienced some impact on daily life due to the PWS, mostly because of feelings of shame. Thirty-seven percent of patients with hypertrophic PWS reported an impact on daily life, their main complaints being feelings of depression and shame, and remarks from other people. Five percent of patients with hypertrophic PWS tended to stay at home due to their PWS.

### Table 1. Characteristics of all port-wine stains and of hypertrophic port-wine stains specifically

<table>
<thead>
<tr>
<th></th>
<th>All PWS (n=335)</th>
<th>Hypertrophic PWS (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>228</td>
<td>54</td>
</tr>
<tr>
<td>Neck</td>
<td>57</td>
<td>21</td>
</tr>
<tr>
<td>Torso</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Upper extremities</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5%</td>
<td>93</td>
<td>17</td>
</tr>
<tr>
<td>0.5-2.0%</td>
<td>152</td>
<td>27</td>
</tr>
<tr>
<td>&gt;2.0%</td>
<td>90</td>
<td>24</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pink</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>Red</td>
<td>165</td>
<td>34</td>
</tr>
<tr>
<td>Purple</td>
<td>74</td>
<td>30</td>
</tr>
<tr>
<td><strong>Hypertrophy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>267</td>
<td>80%</td>
</tr>
<tr>
<td>Thickened</td>
<td>17</td>
<td>5.1%</td>
</tr>
<tr>
<td>Nodular</td>
<td>27</td>
<td>8.1%</td>
</tr>
<tr>
<td>Thickened + nodular</td>
<td>24</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

This table shows all characteristics of port-wine stains explored in our study population by reviewing the records and photos of port-wine stain patients. PWS = port-wine stain

# Patients can have PWS in more than one location

* Size of the PWS given in percentage of total body surface as measured by the rule of nines

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DISCUSSION

In this study, we show that hypertrophy is a common development in PWS, affecting 20% of all PWS patients and 71% of patients above 50 years of age. Increasing age was significantly associated with hypertrophy. Previous studies on hypertrophic PWS

Figure 2. Distribution of port-wine stain (PWS) patients in different age groups. Dividing all PWS in different age groups, most patients with PWS are fairly young. However, when dividing patients with hypertrophic PWS into the same age groups, only a small percentage is younger than 20 years old. Most patients with hypertrophic PWS were over 40 years old. The figures indicate the percentages of the whole PWS group and percentages of the hypertrophic PWS group.

Figure 3. Distribution of types of hypertrophy in port-wine stains (PWS). Dividing the different types of hypertrophy in age groups, diffuse thickened hypertrophy is seen in all age groups. Nodular hypertrophy, and the combination of the both types, is mostly seen in patients over 40 years old. The figures indicate the percentages of the whole nodular PWS group, percentages of the whole diffuse thickened PWS group and percentages of the whole group with combined hypertrophic PWS.
show numbers that differ widely. Age may partly account for these differences, since Klapman et al. found the highest percentage of hypertrophy (40%) in a relatively older population (median age of 29 years). In contrast, Mills et al. investigated a population of approximately 22 years of age and reported hypertrophy in only 10% of patients. Previous studies did not report the age of onset of hypertrophy. The median age of onset reported by our patients was 31 years (0-65), which is at variance with the general opinion that hypertrophy usually does not occur until the 4th or 5th decade of life. While the first signs of hypertrophy seem to appear early, it is obvious that hypertrophy becomes a major issue above the age of 50 years, affecting 71% of patients. These high figures suggest that eventually almost all PWS become hypertrophic. Minkis et al. suggested that late and inadequate laser treatment of PWS may increase the risk for hypertrophy. Due to inadequate matching of our patients and unreliable information on previous laser therapy, it was not possible to assess a preventive effect of previous laser therapy on the development of hypertrophy.

It is not clear whether location is of importance for development of hypertrophy. In our population, PWS on the extremities seemed to be less predisposed to hypertrophy. However, it is difficult to draw conclusions when the numbers are so small (Table 1). In the multivariate analysis, only PWS on the neck seemed to have a higher risk for hypertrophy. We found that hypertrophy is more common on the face than elsewhere on the body, but PWS in general are more commonly seen on the face. Other studies show the same figures for location of PWS. Color seems to be related to the occurrence of hypertrophy as 94% of hypertrophic PWS were red or purple. Hardly any of the hypertrophic PWS were pink, as was reported in previous studies. On the other hand, only 39% of all purple PWS were hypertrophic. In the multivariate analysis, purple and red PWS were at a significantly higher risk for hypertrophy compared to pink PWS.

We classified hypertrophy as either thickened or nodular, as did Klapman et al. In 1984, Finley et al. differentiated a cobblestone pattern (thickened PWS) from localized tumor formation (nodules). Other nomenclature used to denote nodular hypertrophy has included blebbed or papular PWS. We observed nodules mostly in patients over 30 years. Diffuse thickened hypertrophy (mostly deeper thickening; Fig 1b) was present at a younger age, as was also observed in Klapman’s study. Finley et al. described nodules in the flat PWS of young patients as well as in the thick PWS of older patients. Remarkably, we found a differential median age of onset for thickened PWS (12 years) and nodular PWS (39 years) which may imply a different pathophysiology. To date, little is known about the mechanisms involved. According to the literature, the term diffuse thickening describes both larger plaques and deeper situated thickening of underlying structures. These two categories could represent different forms of diffuse thickening. Future studies on the pathophysiology of hypertrophic PWS should differentiate between diffuse thickened and nodular PWS, and perhaps also between the two variants of diffuse thickened hypertrophy, as different pathomechanisms may require a different therapeutic approach.

As seen in other studies, we found an almost equal male-female distribution in hypertrophic PWS, while there was a female preponderance (69%) in the whole study.
population. We believe this female preponderance is because women may be more likely to seek treatment for cosmetic reasons. Hypertrophic PWS may be regarded as a problem for both men and women.

We expected hypertrophy to have an additional negative impact on daily life for PWS patients. Many patients complained of discomfort or even bleeding, when shaving their beard in the hypertrophic part of the PWS, or when combing their hair if the scalp was involved. Although 1/3 of patients reported some impact on daily life, there was little difference between PWS patients with or without hypertrophy (37% versus 31%). There are some limitations to the present study. First of all, the figures are biased as our data came from a tertiary laser centre. Selection of the more difficult to treat hypertrophic PWS may have occurred. The female preponderance was probably also the effect of selection bias. Secondly, the retrospective design is a limitation. Historical data regarding details of treatment and onset of hypertrophy in the PWS relied on the memory of patients and could be inaccurate.

Pulsed dye laser therapy is the standard of care for PWS. Hypertrophy, however, does not respond satisfactorily to treatment with this laser. Previous studies have investigated the response of hypertrophic PWS using different settings of PDL, long-pulsed Nd:YAG, CO$_2$ and (long-pulsed) alexandrite lasers, with various outcomes. $^{18-23}$

Patients should be informed about the natural course of PWS and more attention needs to be drawn to therapy and prevention of hypertrophic PWS.

REFERENCES


