PHACES syndrome: Diode laser photocoagulation of intraoral hemangiomas in six young patients

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- Rare disease
- Vascular tumor

**Abstract**

**INTRODUCTION:** The acronym PHACES describes the association of posterior fossa malformations, facial hemangiomas, arterial anomalies (cardiovascular or cerebrovascular), coarctation of the aorta and cardiac defects, eye abnormalities, and sternal or ventral defects. In this study we report on 6 patients affected by the PHACES syndrome and showing 34 intraoral hemangiomas (IH), treated by diode laser photocoagulation (DLP).

**CASE PRESENTATION:** IH appeared as red-bluish soft masses, smooth or lobulated, from a few millimetre to several centimetres in size, covered by intact mucosa and blanching on pressure. IHs were treated by DLP with 320 μm fibres at a wavelength of 800 ± 10 nm. The diode laser techniques applied were: Transmucosal DLP (DLTP), a no-contact technique in which laser energy is delivered by a flexible optic quartz fiber, which is kept 2–3 mm apart from the lesion, and Intralesional DLP (DLIP), in which the fibre is introduced into the lesion through a transmucosal access. DLTP was used for 20 flat, superficial IHs and, after a variable number of laser sessions (average = 3) depending on the size of the lesion, 65% completely regressed, while in the remaining 35% shrinkage of the lesion was achieved with minor and few complications.

The remaining 14 deep/multi-lobulated IHs were treated by DLIP, resulting in complete regression of 79% of them.

**CONCLUSIONS:** DLP techniques are an effective and minimally invasive procedure for IH in patients with PHACES, in consideration of the multiple lesions to treat, of the necessity of multiple interventions and the higher compliance of the patients.

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**1. Introduction**

PHACES is an acronym which refers to a rare syndrome characterized by posterior fossa defects, facial hemangiomas, arterial lesions, cardiac abnormalities, eye anomalies and sternal cleft [1,2]. Firstly described by Frieden in 1996 [1], this syndrome shows predilection for the female gender (M:F = 9:1) [3,4]; there is no evidence of familial tendency [5].

Single/multiple facial hemangiomas are the most important clinical manifestation of PHACES. Hemangiomas manifest during the first weeks of life as teleangiectasias or erythematous plaques; subsequently, they increase in size (>5 cm), and converge together, occupying one or more distinct segments: fronto-temporal, maxillary, mandibular or fronto-nasal [6]. In 80% of the cases, hemangiomas in the mandibular region are associated with sternal clefts [7] and cardiovascular abnormalities [2,7,8]. Hemangiomas could completely or partially regress during the first decade, thus acquiring a port-wine like aspect.

The most common extracutaneous features are: cerebrovascular, structural brain and cardiovascular abnormalities [9].

Cerebrovascular anomalies consist in abnormalities of major cerebral arteries and are divided into four categories: dysplasia, narrowing, aberrant course/origin and persistence of embryonic anastomoses [8].

A spectrum of congenital structural brain abnormalities have been described in the PHACES syndrome, the most common of which involving the cranial posterior fossa [8].
Table 1
Diagnostic criteria for PHACES syndrome.

| Organ system            | Major criteria                                                                 | Minor criteria                                                                 |
|-------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Cerebrovascular         | Anomalies of major cerebral arteries:                                          | Persistent embryonic artery other than trigeminal artery:                     |
|                         | Dysplasia of the large cerebral arteriesa                                      | Proatlantal intersegmental artery (types 1 and 2)                             |
|                         | Arterial stenosis or occlusion with or without moyamoya collaterals            | Primitive hypoglossal artery                                                  |
|                         | Absence or moderate to severe hypoplasia of the large cerebral arteries       | Primitive otic artery                                                         |
|                         | Aberrant origin or course of the large cerebral arteries                      |                                                                                |
|                         | Persistent trigeminal artery                                                  |                                                                                |
|                         | Saccular aneurysms of any cerebral arteries                                  |                                                                                |
| Structural brain        | Posterior fossa anomaly                                                       | Enhancing extra-axial lesion with features consistent with intracranial       |
|                         | Dandy-Walker complex                                                         | hemangioma                                                                     |
|                         | Unilateral/bilateral cerebellar hypoplasia/dysplasia                         | Midline anomalyc                                                              |
| Cardiovascular          | Aortic arch anomalies:                                                        | Neuronal migration disorderd                                                  |
|                         | Coarctation of aorta                                                          |                                                                                |
|                         | Dysplasiaa                                                                    |                                                                                |
|                         | Aneurysm                                                                     |                                                                                |
|                         | Aberrant origin of the subclavian artery with or without a vascular ring      |                                                                                |
| Ocular                  | Posterior segment abnormalities:                                              | Anterior segment abnormalities:                                              |
|                         | Persistent fetal vasculature (persistent hyperplastic primary vitreous)       | Sclerocornea                                                                  |
|                         | Retinal vascular anomalies:                                                   | Cataract                                                                       |
|                         | Morning Glory disc anomaly                                                    | Coloboma                                                                       |
|                         | Optic nerve hypoplasia                                                        | Microphthalmia                                                                 |
|                         | Peripapillary staphyloma                                                      |                                                                                |
|                         | Coloboma                                                                      |                                                                                |
| Ventral or midline      | Sternal defect                                                                | Hypopituitarism                                                                |
|                         | Sternal cleft                                                                 |                                                                                |
|                         | Supraumbilical raphe                                                         | Ectopic thyroid                                                                |
|                         | Sterna defects                                                                |                                                                                |

a Includes kinking, looping, tortuosity, and/or dolichoectasia.
b Internal carotid artery, middle cerebral artery, posterior cerebral artery, or vertebrobasial system.
c Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia.
d Polymicrogyria, cortical dysplasia, or gray matter heterotopia.

Fig. 1. IH on the right cheek before (1a) and after Diode Laser Transmucosal Photocoagulation (1b).

Fig. 2. A gingival lesion in region 2.1–1.8 before laser treatment (2a), after 2 Diode Laser Intraliesional Photocoagulation sessions (2b) and after complete healing (2c).
The most important cardiovascular anomaly associated with PHACES is coarctation of the aorta, which occurs in 14.5% of the affected patients [8]. Abnormalities of the eye are rare and most frequently consist in microphthalmia and exophthalmus [9,10]. Ventral development defects consist of sternal clefting and supraumbilical abdominal raphe [10]. Other extracutaneous manifestation of PHACES syndrome is intraoral haemangioma (IH), which has been only occasionally reported in the English literature.

According to the consensus statement on diagnostic criteria for PHACES syndrome, the diagnosis requires the presence of segmental haemangioma of the head, greater than 5 cm, plus one major criterion or 2 minor criteria, as illustrated in Table 1 [10].

The PHACES syndrome may show variable clinical presentation, according to a major and a minor phenotype, the former being characterized by several life-threatening abnormalities, which could kill the patient within the first years of life, the latter manifesting less serious anomalies, which allow patients to reach adulthood.

This work was aimed at describing the clinical features of the vascular lesions occurring in 6 young patients affected by the PHACES syndrome, and to illustrate the efficacy of diode laser photocoagulation for the treatment of IH.

2. Case presentation

This study was carried out in accordance with the code of ethics of the world medical association (Declaration of Helsinki). The patients released informed consent on diagnostic and therapeutic procedures and for the possible use of biological samples for research purposes.

In this study we report the cases of 6 PHACES patients (average age: 17.5 years), 2 males and 4 females, who collectively were affected by 34 Intraoral Hemangiomas.
treated by DLIP. After a variable number of DLIP sessions (average = 4), 79% (lower lip: 4, upper lip: 3, 1 fornix, gingiva: 1 and cheek: 2) completely regressed, the remaining 21% having presented shrinkage of the lesions and reduced complications (Figs. 2 and 3). The follow-up period after the treatment was 18–72 months (average: 45 months) with no evidence of recurrences of the healed lesions.

3. Discussion

Facial hemangiomas are the most common PHACES syndrome features. One of the most common extracutaneous localizations of hemangiomas is the oral cavity, although rarely reported in the English literature. PHACES IHs, like those in non-syndromic patients, appear as red-blush soft masses, smooth or lobulated, often covered by intact mucosa[12]. Those located on lower lip patients, appear as red-bluish soft masses, smooth or lobulated, of hemangiomas is the oral cavity, although rarely reported in

In the past years, a lot of surgical and non-surgical treatments were tested for the management of hemangiomas. In view of the haemorrhagic risk and high invasiveness related to surgical excision, attention was paid to the possible alternative use of pharmacological and/or minimally invasive interventions. Several drugs have been tested, such as: propranolol[13,14], steroids[15], vincristine [16] and bleomycin [17], which were proved effective on hemangiomas in their proliferative phase, and recommended in paediatric patients affected by PHACES syndrome. Laser photocoagulation has been considered an effective and non-invasive option for the treatment of adult PHACES patients with IHs without relevant side effects and toxicity [18,19].

In view of hemangiomas containing high amounts of haemoglobin absorbing in the spectral range of about 400–1100 nm, Diode Laser with a wavelength of 800 ± 10 nm was chosen because of its affinity to oxyhaemoglobin, producing photothermalysis, erythrocytes microagglutination and vessel obliteration.

The diode laser therapeutic approach to vascular lesions is based on different techniques, such as transmucosal photocoagulation (DLTP) or intraleisional photocoagulation (DLIP). DLTP, preferred for flat superficial/reddish IH, being a no contact technique, resulted a minimally invasive treatment, with high rate of complete regression (65%), low incidence of post-operative pain, bleeding and oedema (15%). The DLIP technique, though at higher risk for post-operative pain, bleeding and oedema, in comparison with DLTP (42.85%), was chosen for deeper lesions and resulted in complete regression of 79% of the lesions.

The additional use of the gel compound of hyaluronic acid and amino acids reset to zero post-operative complications and allowed faster healing of the lesions.

4. Conclusions

Diode laser photocoagulation techniques have been proved a very effective and minimally invasive treatment for PHACES IHs, considering the presence of several concomitant lesions and the necessity of numerous interventions.

Conflict of interest

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

Sources of funding

All Authors declare no sources of funding or any study sponsors.

Ethical approval

This study was carried out in accordance with the code of ethics of the world medical association (Declaration of Helsinki) and approved by our institution ethical committee (study nr 4576 – Prot. 1443/C.E.). The patients released informed consent on diagnostic and therapeutic procedures and possible use of biologic samples for research purposes.

Consent

The patients released informed consent on diagnostic and therapeutic procedures and possible use of biologic samples for research purposes.

Authors contribution

Gianfranco Favia: study concept or design, data collection, data analysis or interpretation, writing the paper, final revision.

Luisa Limongelli: study concept or design, writing the paper.

Angela Tempesta: study concept or design, writing the paper.

Matteo Favia: study concept or design, writing the paper.

Eugenio Maiorano: study concept or design, data collection, data analysis or interpretation, writing the paper, final revision.

Guarantor

The corresponding author is the guarantor of submission.

Ethical standards

We hereby declare that this paper has not been previously published or submitted elsewhere, the authors have read and approved its content and all authors do not have competing interest to declare.

Also,
- The work compiles with the ethical policies of the journal.
- It has been conducted under internationally accepted ethical standards.
- All diagnostic and therapeutic procedures were carried out according to “standard good clinical practice”.
- No experimental procedures were carried out that would require approval by an ethical committee.
- Data from all patients included in this study were treated ano-

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