CONTEMPORARY POSSIBILITIES OF TREATING VASOFORMATIVE TISSUE TUMOURS

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The authors present a review of up-to-date methods of vasoformative tissue tumours treatment. The necessity to choose the best therapy and the risks of single therapeutical procedures are pointed out.

Vasoformative tissue tumours, haemangiomas especially, are the most common benign tumours. Their development, diagnostics and therapy has so often been discussed in professional literature that the whole problematic should seem to be definitely solved. Clinical practice, however, disproves these opinions, as contemporary clinical investigations and introduction of new therapeutic procedures have confirmed.

In many cases haemangiomas are diagnosed in childhood. We can find them in 10–12% normally delivered and as much as 22% preliminary delivered children with a delivery weight less than 1000 g. The tumours occur three times more often in girls⁶⁴.

Histologically, these tumors are either hamartomas, or true tumours. They are characterized by quick proliferation in the period between 8 and 18 months after delivery. The proliferation can during the following 5–8 years be changed by slow regression (phase of involution). Total tumour regression is possible in 50–70% of cases. Exceptions are tumours located in orofacial region. Many physicians still underestimate the importance of this disease. Patient can be seriously damaged by neglect or by missing the period, suitable for the treatment of proliferating haemangiomas. Multilocular haemangiomas of the skin (diffusal haemangiomatosis) and large haemangiomas of the face are often accompanied by visceral haemangiomas (Parkinson-Weber Syndrome). This is the reason why sucklings suffering multilocular haemangiomas of the skin should undergo screening of abdominal cavity by means of sonography or dopplerometry⁹⁸. Large haemangiomas of the neck and face can be connected with multiple anomalies, known as PHACES Syndrome (malformation of the posterior cranial fossa, haemangiomas of cervicofacial region, arterial malformations, anomalies of the heart, eyeballs, thoracic and abdominal clefts, etc.)⁷⁹. Other syndromes, connected with haemangiomas, are e.g. Sturge-Weber Syndrome, Gorau Syndrome, Klippel-Trenaunay Syndrome, etc. Central maxillary haemangioma combined with retinal angiomatosis is known as

Von Hippel Disease. Other important syndromes are the Louis-Bar Syndrome (ataxia and teleangiectasia) and the Kasabach-Meritt Syndrome (thrombocytopenia with coagulopathy). Venous and arteriovenous malformations create a very important group, too^{20, 21, 31, 39, 43, 73, 76, 92}.

Tumours can be classified both from the point of view of histopathological structure and/or clinical picture. According to histopathological structure we can differentiate between capillary and cavernous haemangiomas. Clinical classification of these tumours consists of four groups: naevus flammeus, haemangioma simplex, haemangioma cavernosum and haemangioma faciei⁹⁶.

In childhood, haemangiomas have various clinical pictures. Capillary “strawberry” haemangioma mainly localized on the head and neck can be diagnosed mostly in neonatal period. Cavernous haemangiomas can appear either in neonatal period or during the first six months in any area of the human body (liver, pericardium, orbit, subglottic area etc.)^{63, 81, 84}. “Alarming” haemangiomas (Enjolras et al.) are called the tumors which damage important “vital” structures and endanger the child's life by serious complications^{32, 33, 79}.

Large tumours or vascular malformations of the face can be very difficult to treat. New ways of treatment must be looked for because the mortality of these diseases varies between 40–60%^{3, 56, 57}. A tumour, which in its substance is benign, can endanger the patient's life by its malignant localization (orbit, liver, etc.) The logical consequence is a highly varied spectrum of treatment methods. Beside „classical“ therapies (surgery, embolization of tumor caverns, sclerotherapy, cryotherapy, use of corticosteroids) other new up to date methods have appeared⁹⁹. In some patients contemporary treatment methods fail because of the tumour's size, localization or resistance to treatment. In fact, the rule “primum non nocere” must be respected especially in children, where a mutilating surgical procedure in the face sometimes combined with massive bleeding could represent

an unacceptable risk both for the surgeon and the small patient. There are similar situation's in the case of large, particularly cavernous haemangiomas with the above mentioned "malignant" localization in adults. The treatment strategy must be strictly individual. It is necessary to use combined methods so as to get optimal treatment results and minimize complications and disadvantages of the single ways of treatment². In spite of these possibilities and progress in modern health care there are some problems hard to solve at the contemporary level of knowledge. We are sure that it is just here where new space opens for new, up-to-date therapeutic procedures as e.g. treatment of areal haemangiomas (naevus flammeus) by means of a colour laser, systemic therapy of „alarming“ haemangiomas by means of Interferon alfa 2a or embolization of tumours after preliminary super-selective arteriography.

There are many less or more invasive methods in conservative treatment of haemangiomas which are mentioned in the following table:

A review of therapeutic procedures in the treatment of haemangiomas

- Local ways of treatment:
 - Laser therapy
 - Radiotherapy
 - Electrocoagulation
 - Sclerotization (Aethoxysclerol)
 - Cryosurgery
 - Therapeutic embolization
 - Surgery
- Systemic ways of treatment:
 - Corticoid administration
 - Systemic application of interferons

Under the level of contemporary experience, surgery still holds a dominant position on the scale of therapeutic possibilities. Surgical treatment is the procedure of choice regarding to the type, location and size of the tumour. Large haemangiomas are often a great therapeutic problem because of the high risk of peri- and postoperative bleeding. Surgical procedure consists in tumour extirpation (often after sclerotization, embolization or external carotid artery ligation). Large haemangiomas of the orbit can be, in extreme cases, removed only using radical exenteration of the orbital tissues. Surgical treatment of a large haemangioma of the face must be followed both by reconstruction and rehabilitation. A surgery brings about many risks. In many cases, it has to be completed or replaced by other therapeutic procedures. We use it for all small and medium sized cavernous and capillary haemangiomas up to the size of a hazelnut. The extirpation is usually a single, only larger tumours require gradula intervention⁵⁶.

The next invasive method of treating haemangiomas is embolization. It has two aims: when the emboli penetrate the tumour tissue with large enough stalks, it has a therapeutic effect and reduces or stabilizes of the size of the cavernoma,

making the later classical surgery easier^{62, 80, 105}. When the embolizing particles only obturate the arterial stalk of the haemangioma, embolization has a hemostatic effect and it is performed as a preparation for an operation with an imminent blood loss. The preparations currently used are Gellaspon, Bucrylat or Histoacryl. Another possibility are silicon balls with baryum. To prove arteriovenous short circuits in orofacial area phlebography, arteriography or selective arteriography and dopplometric examination are used^{69, 73}. Artificial embolization in the area of the external carotid must be preceded by carotid angiography^{19, 20, 21, 22}. A surgeon should be present during the examination, who assisted by a radiologist, will decide about further therapy. Large tumours, which are difficult to remove surgically, can be treated by embolization. Its extent is determined by the character of the vascular supply of the tumour – i.e. by the site and size of the supplying blood vessels. This method is used first of all for terating hemangiomas diffusely infiltrating into the soft tissues of the face and neck⁵⁹.

Cryolization is based on tissue destruction by necrotizing temperatures (-20°C – -196°C) causing irreversible necrosis followed by elimination of the necrotic tissue. The cryocycle must usually be repeated. The depth of necrotization is up to 10 mm. The best freezing time is 30–40 seconds at -186°C .

Although cryodestruction is quite an old method⁸³, it still has its justified use^{10, 30, 37, 41, 61, 75, 91}. In this country, those who have got large practical experience with cryotherapy are especially Průcha, Kostřica, Žaloudík and Šebestová^{82, 90}. We recommend this method particularly for cavernous haemangiomas of the tongue, where we have had almost a hundred per cent success^{53, 89}. The method is suitable for high risk patients, for elderly patients, and in cases where for some reason, no other method can be used. In orofacial area it brings about not only a therapeutic but also aesthetic success, except for skin hemangiomas, where it can leave aesthetically disturbing scars⁶⁶.

One of the least invasive methods of treating tumours is using a laser ray^{5, 8}. Laser therapy is a relatively new method. It is based on maximum absorption of laser energy by target chromophors with a minimum thermal damage to the surrounding tissues. This phenomenon is explained in the theory of selective photothermolysis (Anderson, Parish). According to the type of the medium used we can divide lasers into several groups:

1. Gas – argon, CO_2 , He-Ne laser
2. Solid – Nd: YAG laser, semiconductor lasers
3. Liquid – dye laser (laseractive atoms are dissolved in a liquid)

The most common surgical laser is the CO_2 laser^{17, 100}. It is used for parenchymatous organs, because it coagulates blood vessels. The flashlamp pumped dye laser has recently been recommended for vasoformative tissue tumours^{4, 9, 24, 28, 35, 36, 60}. We have used the Chromos 585 dye laser Sharplan (wave lenght 585 nm, energy density $2.5\text{--}10\text{ J/cm}^2$). We regard the dye laser as suitable for all

types of angiomatous naevi, hemangiomas (especially skin forms), naevus flammeus in the face and on the neck, including the Sturge-Weber Syndrome and teleangiectasis.

Non-invasive methods of treating vasoformative tissue tumors are radiotherapy, sclerotization and systemic cures with corticoids or interferons¹³. Apart from surgery, radiation therapy in orofacial region occupies an important place, though only in strictly defined indications. The kind of treatment, irradiation source and especially the dose and fractionation of the irradiation as well as the time of irradiation and the extent of the irradiated tissue are usually decided upon by an oncologist and radiotherapist. The aim of radiotherapy is elimination of the tumour tissue without early or late damage to surrounding healthy tissues. For the oral cavity and face, this method is only used in case of a total failure of other methods available for the proliferatively growing large haemangiomatoses of the head and neck. Endothelial cells of the haemangiomas are of embryonal nature and they are very sensitive to radiation. During maturation their sensitivity decreases. Therefore the aim of irradiation is not their fast destruction, but an induction or acceleration of their involution. Controversial opinions on children's hemangioma treatment were pointed out by Bek and Koutecký, who themselves recommend radiation therapy in indicated cases^{14, 15, 16}. For capillary "strawberry" haemangiomas, which occur mostly in the area of the head and neck and initially grow very fast, low dose therapy is recommended only in complicated cases (amblyopia).

One of the conservative methods of treating vasoformative tissue tumours is sclerotization. This method consists in intratumorous application of sclerotizing preparations⁴⁷, which irritate the intima and cause reactive thrombophlebitis with tissue proliferation and scarring⁵¹. The best of all agents available is Aethoxysklerol-Kreussler in 0.5–3% concentration – which we have been using for twenty years⁴⁹. No side effects have been registered except for local swellings due to histamine-type activity. That can be blocked with a suitable antihistaminic⁵⁰. Sclerotherapy has been worked out in detail at our Department. We sclerotize vasoformative tissue tumours wherever surgical intervention is not suitable because of the size or the location of the tumour, e.g. in large cavernous haemangiomas of the tongue, tumours in the mouth corner, or hemangiomas of the pharyngeal wall. The next indication is demarcation of the tumour before the operation in order to reduce its size, to decrease operation bleeding and to cure the residua left after tumour extirpation. We use sclerotization to treat circumscribed recurrences of vascular angiomas. In some cases, sclerotization is a method of choice, especially in aesthetically important parts of the face, in others it is an alternative method^{44, 48}.

Systemic corticoid therapy has become dominant in haemangioma treatment in children, though its effect upon the tumour tissue has not been cleared up³⁸. Recommended doses are 2–3 mg/kg (sometimes up to 5

mg/kg) a day. In one third of the patients this treatment leads to a dramatic reduction of the haemangioma within a few days, in about one third of the sucklings the tumour stops growing and in the remaining children the response is very poor or none. In spite of undesired side effects most children take this treatment well and their retarded growth is corrected after the end of the therapy. Large doses of intravenous methylprednisolon have been used for life-threatening and "alarming" haemangiomas and in cases of the Kasabach-Meritt phenomenon. To small, localized skin haemangiomas corticosteroids can be applied directly into lesions. The amount of triamcinolon should not exceed 3–5 mg for one dose. But this treatment is counterindicated with haemangiomas of periorbital area (skin atrophy, necrosis and occlusion of the retina artery with following blindness⁹³). Another recommended indication are vasoformative tissue tumours situated in the parotis and parenchymatous organs. We were forced to use systemic and intratumorous corticoid therapy (local application of Urbason, systemic use of Triamcinolon) for a six-month-old child with large hemangiomatosis in the face, oral cavity and neck. Because the tumour proliferated into the nasopharynx we had to combine the treatment with actinotherapy.

Interferons (IFN) have recently been advocated for their antiangiogenic effect in systemic therapy of haemangiomas, above all for "alarming" and life-threatening tumours^{7, 26, 29, 79, 101, 102, 103, 104}. Although we still do not know exactly the mechanism which controls the growth and regression of hemangiomas, the latest knowledge of angiogenesis and blood vessels evolution helps to understand it better. Vasculogenesis relates to the processes in which new vessel develop from the precursors of endothelial cells, whereas during angiogenesis the already existing vessels mature.

The antiangiogenic effect of interferon was described as early as 1970 by Folkman. IFN inhibits angiogenic molecules of the tumour cells^{11, 34}. Inhibitors are able to penetrate into the finest capillaries of the blood system⁷⁸. The ability of IFN to potentiate tumoricidal activity of some cytostatics has its share in the anti-tumour effect⁷². A promising factor is the strong synergism between alpha IFN and platinum derivatives, but also between IFN and retinoid acid derivatives which were proved to increase S-tat 1 expression. We succeeded in verifying the effect of alpha 2a interferon upon the vasoformative tissue tumours, inoperable because of their size or location (orbit), when preparing patients for a surgery (reduction of bleeding), or in cases when the recommended therapy had failed⁵⁸. New knowledge of the transmission of the activating signal of the IFN led to a change in the dosage. One million units was found to be enough as a maintenance daily dose. New dosing can in these cases reduce the undesired effect ("flu syndrome", neutropenia, liver enzyme abnormalities and, for children, neurological complications). This type of therapy can be performed only where its success can be assessed from some specific cellular signs of angiogenesis (e.g. urine based fibroblastic growth factor). Such findings

could help to determine the optimal doses of the medicine. No interferon therapy can be started without the agreement of both experts (pediatrist, dermatologist, maxillofacial surgeon, oncologist) and the child's parents.

Despite many therapeutic alternatives, the treatment of vasoformative tissue tumours brings about a lot of risk and problems. Therefore the indication and the type of therapy must be a result of team cooperation.

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