New aspects of pathogenesis of juvenile angiofibroma

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For over 150 years the aetiology of juvenile angiofibroma has been addressed in numerous theories, but actual details remained unknown. Interesting new findings, reviewed here, are beginning to elucidate the aetiology of this fascinating tumour.

Juvenile angiofibroma is a rare but unique neoplasm because of its typical clinical characteristics. The tumour arises in the posterior nasal cavity close to the sphenopalatine foramen, almost exclusively in adolescent males. It derives its main blood supply from the sphenopalatine artery, with possible additional blood supply from the internal carotid artery. Although the tumour, with its typical irregular vascular endothelial-lined spaces embedded in a fibrous stroma, is regarded as a benign tumour, juvenile angiofibroma not infrequently exhibits an aggressive growth pattern with spread through natural fissures and foramens. Occasionally intracranial tumour extension has been observed (Schick and Kahle, 2000).

These features have stimulated questions about the aetiology of juvenile angiofibromas for more than 150 years, but despite suggestions of numerous theories, the aetiology of this unique tumour remained unknown. The first theories in the 19th century suggested a fibrous tumour origin, while in the 20th century theories focussed on a vascular tumour origin (Schick et al, 2002b). Other explanations involve tumour originating from non-chromaffin paraganglionic cells present at the terminal end of the maxillary artery, ectopic vascular tissue growing as a result of alterations in pituitary activity or misplaced genital erectile tissue (hamartoma). These theories illustrate the varied thoughts on tumour pathogenesis. None of the numerous theories were generally accepted as they were only able to explain single typical tumour features rather than all of them.

JUVENILE ANGIOFIBROMA: A VASCULAR MALFORMATION?

Detailed immunohistochemical and electron microscopic examinations of the vascular architecture found various morphological irregularities. As a result of these findings it was suggested that juvenile angiofibromas were vascular malformations (Beham et al, 2000). This suggestion was strongly supported by further embryological considerations. Tumour development based on incomplete regression of the first branchial arch artery would explain the characteristic tumour blood supply as well as the typical tumour origin close to the sphenopalatine foramen (Schick et al, 2002b). The first branchial arch artery arises in embryogenesis between day 22 and 24, forming up a temporary connection between the ventral and dorsal aorta. This vessel ensures cerebral blood supply in this early developmental stage.

With regular development of the common carotid artery the first branchial arch artery usually regresses via formation of a vascular plexus. Regression of this plexus starts at the connection to the later internal carotid artery and is completed at the site of the sphenopalatine foramen. Parts of the first branchial arch artery participate at this site in the formation of the maxillary/ sphenopalatine artery. Indeed Harrison (1987) described vascular endothelial-lined spaces close to the sphenopalatine foramen in a male and a female fetus. They can be considered as plexus remnants of the first branchial arch artery.

Tumour development from such plexus remnants deriving from incomplete regression of the first branchial arch artery (atavism) is therefore an excellent explanation for a tumour originating close to the sphenopalatine foramen with typical tumour blood supply from the sphenopalatine or maxillary artery. Furthermore blood supply from the internal carotid artery as a result of possible plexus remnants connecting the tumour vascular network with the internal carotid artery may also explain why some juvenile angiofibromas derive

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their blood supply from the internal carotid artery, even though they are located far from this major vessel (*Figure 1*).

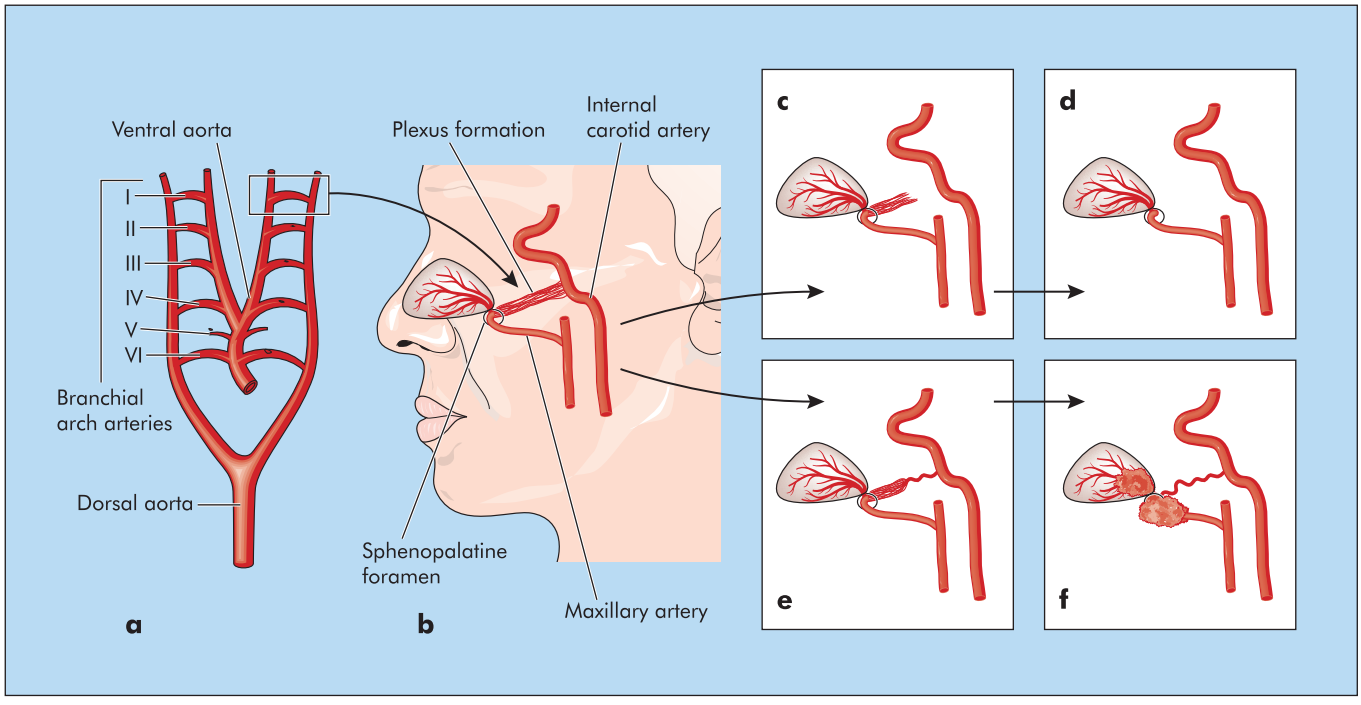
The two remaining tumour characteristics of almost exclusive tumour manifestation in adolescent males and frequent aggressive tumour growth are not explained by the assumption of an atavism of the first branchial arch artery. To explain these characteristics a closer look at the genetic and molecular alterations in juvenile angiofibromas is necessary.

GENETIC AND MOLECULAR INVESTIGATIONS IN JUVENILE ANGIOFIBROMAS

So far only a few genetic and molecular studies have been performed in juvenile angiofibromas. Immunohistological investigations showed activated transforming growth factor-β1 (TGF-β1) in both the stromal and endothelial cells of 19 juvenile angiofibromas (Dillard et al, 2000). In the search for possible Ki-ras and Ha-ras abnormalities codons 12, 13, 59 and 61 of these genes had been analysed in juvenile angiofibromas but no mutations were found (Coutinho et al, 1999). A loss of the glutathione-S-transferase M1 gene known to be associated with an increasing risk of developing a malignancy of the upper aerodigestive tract has been detected in three out of eight juvenile angiofibromas (Gautham et al, 2002). In addition, alterations in the insulin-like growth factor-II (IGF-II)/H19 imprinted region with IGF-II overexpression in eight out of 22 juvenile angiofibromas (36.4%) and H19 overexpression in seven out of 19 juvenile angiofibromas (36.8%) have been reported (Coutinho-Camillo et al, 2003). However, the significance of these findings in the pathogenesis of juvenile angiofibromas is unclear.

Clinical observation of juvenile angiofibroma manifestation in patients with familial adenomatous polyposis coli (APC) (Giardiello et al, 1993) has implicated the APC gene in the pathogenesis of juvenile angiofibroma. Mutations or allelic losses of the APC gene causes a failure to degrade β-catenin which results in nuclear β-catenin accumulation. Mutations in the β-catenin gene itself can also lead to stabilization of the β-catenin protein. Indeed, while no alterations of the APC gene were detected (Guertl et al, 2001), β-catenin

Figure 1. Regular development and regression of the first branchial arch artery (a–d) and atavism of plexus parts derived from the first branchial artery (e–f). a. During embryogenesis the branchial arch arteries temporarily connect the ventral and dorsal aorta. b. Regression of the first branchial arch artery takes place via plexus formation which connects the vascular components of the later maxillary artery and the internal carotid artery. c. Plexus regression starts at the side of the internal carotid artery, so plexus remnants are finally detected at the sphenopalatine foramen, being involved in the formation of the sphenopalatine artery. d. At the time of birth the regression of the first branchial artery is usually completed. e. Incomplete regression of the plexus deriving from the first branchial artery is suggested to build up the vascular component of juvenile angiofibromas with their typical blood supply from the maxillary/sphenopalatine artery, which would explain persistent vascular connections to the internal carotid artery. f. These form a possible blood supply from this vessel even the tumour is still far distant to it. From Schick et al (2002b).



gene mutations which caused nuclear β-catenin accumulation were found in juvenile angiofibromas (Abraham et al, 2001; Rippel et al, 2003). Nuclear β-catenin accumulation was only detected in stromal cells, which suggested that the stromal rather than the endothelial cells were the neoplastic cells of juvenile angiofibromas (Abraham et al, 2001). This might question the previous assumption of a vascular malformation. Nevertheless cytoplasmic β-catenin accumulation was noted in endothelial cells, indicating that β-catenin mutations are not restricted to stromal cells (Rippel et al, 2003). Furthermore neoplastic potential of stromal cells might occur in conjunction with plexus remnants with the consequence that both cell types are involved in tumour pathogenesis.

Comparative genetic hybridization (CGH) investigations found various genetic alterations in juvenile angiofibromas including gain of chromosome X and loss of chromosome Y (Schick et al, 2002a). These sex chromosomal alterations were confirmed in subsequent fluorescence in-situ hybridization studies. Interestingly the gain of an additional X chromosome observed in five out of seven analysed juvenile angiofibromas leads to two copies of the androgen receptor gene (Xq11-q12). Amplifications of the androgen receptor gene, as seen in prostatic cancer, were not observed (Schick et al, 2003).

In accordance with the finding of an androgen receptor gene increase positive nuclear immunostaining for the androgen receptor protein has been reported in 18 out of 24 juvenile angiofibromas (Hwang et al, 1998) and this finding has been confirmed by the authors' own immunohistological investigations (currently unpublished). These findings indicate that juvenile angiofibromas are androgen-dependent tumours but, taking into account the detected β-catenin gene mutations, an additional molecular aspect underlines the assumption that juvenile angiofibromas are androgen-dependent tumours.

Interestingly, a connection between β-catenin and the androgen receptor has been discovered. β-catenin and the androgen receptor were found to translocate as a complex into the nucleus in tissue samples derived from prostatic cancer and in prostatic tumour cell lines, and β-catenin can act as a co-activator of the androgen receptor (Koh et al, 2002; Pawlowski et al, 2002). So the two alterations on the molecular level found in juvenile angiofibromas so far would both be expected to increase the androgen sensitivity of the tumour, which provides an interesting explanation for the clinical observation of almost exclusive tumour manifestation in adolescent males. However, nuclear β-catenin accumulation acting as an androgen receptor co-activator does not only enhance androgen receptor-mediated transcription. β-catenin itself is a member of the Wnt signalling pathway, a known cause of many colon cancers. Nuclear β-catenin complexes with the lymphoid enhancer factor and T-cell factor family to activate transcription of Wnt signalling target genes like the myc-protooncogene, providing an additional growth stimulus.

Based on numerous findings of chromosomal gains and losses in juvenile angiofibromas in CGH studies (Schick et al, 2002a), further genetic studies have to be performed in order to elucidate in more detail the genetic and molecular changes of juvenile angiofibromas. One interesting candidate, for example, is the tumour suppressor gene p53 located on chromosome 17, as the CGH studies showed chromosome 17 losses (Schick et al, 2002a). These findings have already provided convincing explanations of the tumour aetiology and may finally point the way to answering the questions about juvenile angiofibroma pathogenesis.

THERAPEUTIC IMPLICATIONS

The first choice treatment modality is tumour resection. The approaches have become less invasive during the last two decades. While lateral rhinotomy has been replaced by the midfacial degloving approach, numerous tumours have been successfully resected endonasally (Schick et al, 1999). In advanced tumour stages, however, external approaches are still necessary. Radiotherapy and chemotherapy have been used only in single cases and should only be considered for inoperable tumours (Schick et al, 1996).

As treatment is required mainly in adolescent males it is important to use the least traumatic surgical techniques or even to avoid surgery. In this context different hormone treatments in individual patients have been reported in the past. Tumour size reduction was observed after antiandrogen or oestrogen treatment. As no oestrogen receptors have been detected in juvenile angiofibromas, tumour size reduction after oestrogen treatment was postulated to occur as a result of the antiandrogen effect of the oestrogens (Lee et al, 1980). Serious side effects of these hormone treatments limits their use, and they are now mainly avoided. However, antiandrogen therapies with fewer side effects are the subject of intensive research work in the field of

prostatic cancer. If improved antiandrogens become available in the future they should offer important treatment options for juvenile angiofibromas. Reduction of tumour size would allow the use of less invasive techniques, reducing intraoperative blood loss and achieving better cosmetic results. There might be also the chance to use antiandrogens to induce tumour involution in single cases, avoiding surgery all together. Spontaneous regression of juvenile angiofibromas has been seen after adolescence which might be the result of changes in androgen effect on the tumour. **HM**

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Conflict of interest: none.

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KEY POINTS

- Recent findings throw an exciting light on the enigma of juvenile angiofibroma pathogenesis.
- The assumption of a vascular malformation is an interesting theory of tumour origin.
- Atavism of the first branchial arch artery can explain juvenile angiofibromas as vascular malformations.
- Incomplete regression of the first branchial arch artery allows to explain the site of tumour origin and the characteristic tumour blood supply.
- Androgen receptor gene increases in juvenile angiofibromas being associated with increased androgen receptor protein levels indicates an androgen-dependent tumour and fits with almost exclusive tumour manifestation in adolescent males.
- β-catenin mutations are frequent in juvenile angiofibromas and are expected either to activate Wnt signalling pathway regulated genes transcription and to increase via co-activation of the androgen receptor transcription of androgen-dependent genes.