Although molecular and cellular mechanisms concerning the pathogenesis of cherubism have been described, the majority of the literature assumes a primary bone disease. However, this does not explain the clinical characteristics of cherubism. During the discussion regarding the originating tissue for cherubism, a giant cell granuloma is presented as dental mesenchyme that has lost the condensation structure, the epithelial part, through mutation of the binding protein. As this loss only occurs in the bell stage, the morphogenetic expression triggered by the body plan is retained up to full differentiation of the structure. The histological result is a giant cell granuloma, which is derived from myeloid precursor cells with high osteoclastic potential. If one takes into consideration the peculiarities in the developmental biology of the characteristic structural relation of cherubism to tooth budding, then the pathogenesis of the clinical picture can be explained.
Symptoms

Hyckel et al. [2] comprehensively examined the relationship between the histological findings and the clinical symptoms. Since then, these considerations have received no further attention. The SH3BP2 mutation and the histopathological substrate are predominantly at the centre of the deliberations, with the result that at this point, this must be a bone disease.

How can one explain the cardinal symptoms of cherubism against this background?
1. The purely jaw or alveolar process-related symptoms.
2. The time correspondence with odontogenesis of the alveolar ridge.
3. The suspension of the disease pattern in adolescence.

The “bone hypothesis” offers no answer to this question. In contrast, the “tooth formation deficit hypothesis” offers sufficient answers to the questions posed above. When considering the odontogenesis, it is essential, however, that the neural crest-associated processes are included. How can the differences in the evaluation of the pathogenesis be resolved? For this, knowledge of the developmental biology of the teeth and their pattern of expression is essential (Figure 1).

During odontogenesis, the mesenchyme develops through the epithelial part of the cap stage into condensed dental mesenchyme in the bell stage, from which dentin and enamel form through mineralisation. In cherubism, the epithelial / mesenchymal interaction is disrupted. What remains is non-condensed mesenchyme, which, however, still develops the correct gene expression according to the body plan. Thus, it can be morphologically categorised as neither bone nor pulp.

The cause of this is conditional hyperactivity of the macrophages is mutation of the binding protein [8], which arises through the altered differentiation of the myeloidal precursor cells. This leads to increased osteoclastogenesis. Both Ueki et al. [1] and Reichenberger et al. [9] have indicated myeloidal progenitor cells as the source of the clinical picture.

This hypothesis was supported by the statements by Houpis et al. [10]: “…cells originating from the neural crest, particularly cells of the jawbones, the periodontal ligament, or the dental follicle, may be involved in the pathogenesis of giant cell lesions of the jaws”. At the same time, the projected expression mechanisms of PTHr and MSX1 are supported [11]. The loss of MSX-1 antisense, also hypothetically proposed in the same study, is further confirmed by Babaiko et al. [12]: “…that disturbance of the balance between MSX1 S and AS RNA status may be associated with tooth agenesis and bone loss”. Thus, the loss of the epithelial components appears to correspond to AS-RNA.

Conclusion

Cherubism is a self-limiting clinical picture. Although it is rare, it is exactly for this reason that it is becoming important. Understanding of the neural crest related processes is imperative for understanding the pathogenesis. The induced odontogenesis from the alveolar ridge is unique. Thus, a previously not created structure is developed post-partum. For complete understanding of the processes, it would be desirable if this specificity could be detected in animal models in the future.

The information should clarify the value of the clinical progression of cherubism compared with the morphology and molecular biology. At the same time, the factors derived from the neural ridge are particularly important. Hyckel et al. [11] already published a report in 2011 about a similar group of topics based on the development gene-manual development. The main idea quoted by Dob-
Dobzhanski [13] “Nothing in biology makes sense except in the light of evolution” appears to be particularly applicable to cherubism.

An additional interesting relationship can be found in the pathogenetic process with MSX1 expression during bisphosphonate-related osteonecrosis of the jaw (BRONJ) [14]. Unlike in cherubism, here there is the question of a therapeutic option.

References


To cite this article: Hyckel Peter, Schleier Peter, Wehrhan Falk. Cherubism – Pathogenesis still uncertain?. Trends in Dentistry. 2018: 1:1.