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Macrodactyly Update

Macrodactyly has traditionally been considered a specific diagnosis characterized by enlarged digits in the hand or foot that is present at birth and does not undergo malignant degeneration. Involvement of a "nerve territory", most commonly the median nerve in the hand, had been noted. Enlargement of the thumb, index, and middle fingers in some combination is usually associated with a lipofibromatous hamartoma of the median nerve. (Figure 1) Similarly, enlargement of the ulnar digits can be present when the ulnar nerve is involved. (Figure 2)

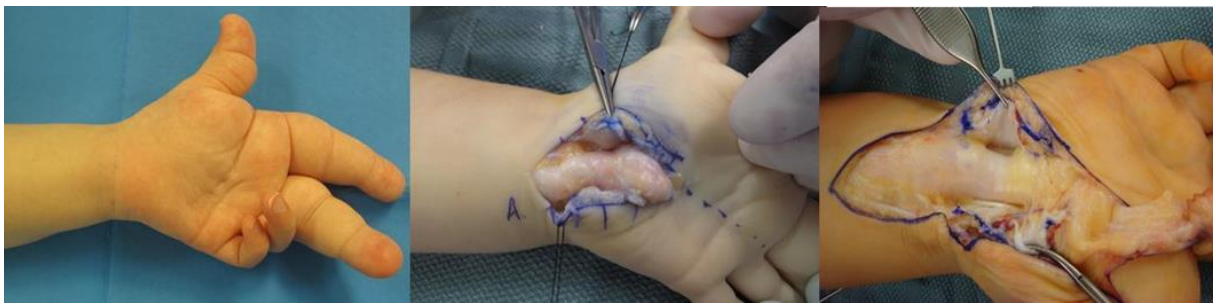

Figure 1. Median nerve distribution macrodactyly; Lipofibromatous hamartoma of the median nerve.

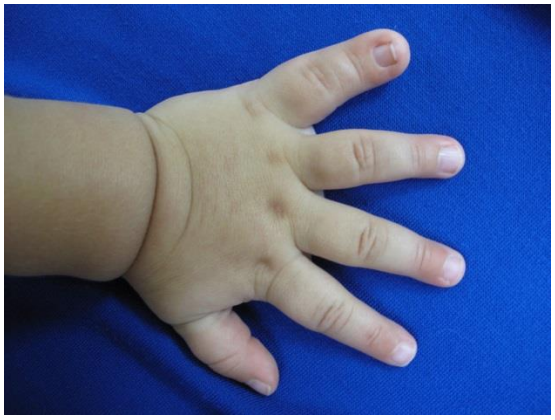

Figure 2. Ulnar nerve distribution macrodactyly.

Macrodactyly most often is confined to a single anatomic region or limb, but cases of more than one site of involvement have been reported. The level of involvement may vary from the distal part of a single digit to an entire hand/foot or limb. All the tissues in the involved area are abnormal. Osseous structures enlarge and joints become stiffened and hyperostotic. Angular deformity of the digits is caused by asymmetric growth of the open physes. The enlargement in the typical case of macrodactyly remains in its original distribution over the growth of the child. The condition may be relatively static, growing in proportion to the child, or may demonstrate progressive enlargement out of proportion to the size and growth rate of the child. When the abnormal tissues grow progressively and extend proximally into uninvolved areas, the condition is termed macrodystrophia lipomatosa.

Other overgrowth conditions have been associated with macrodactyly leading to speculation that there is an underlying diagnosis causing the dysregulation of growth. The development of genome wide parallel sequencing has allowed comparison of DNA from involved and uninvolved tissues. This has led to the identification of a number of somatic mutations, occurring in the post-zygotic early embryo, and causing mosaicism in growth regulation.

Through eloquent genetic sequencing reported by multiple authors, including Rios et al.[1], the genetic abnormality was found to be a gain-of-function mutation in PIK3CA pathway (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase). Because it is a postzygotic mutation some cells carry the mutation while others do not. DNA sequencing of affected tissue will show this PIK3CA mutation, while DNA sequencing of unaffected areas in the same individual will not.

The most recent, significant advance in our understanding is the discovery that macrodactyly is a part of a spectrum of overgrowth disorders related to PIK3CA mutations. PIK3CA-Related Overgrowth Spectrum (PROS)[2] includes macrodystorphic lipomatosis, CLOVES (Congenital Lipomatous Overgrowth, Vascular malformation, Epidermal nevi, Spinal/skeletal anomalies) (Figures 3-4), as well as hemimegalencephaly and others. Interestingly, Luks et al.[3] have recently reported that PIK3CA mutations are present in most isolated lymphatic malformations as well as conditions in which lymphatic malformations are a component.

The clinical presentation of a PIK3CA mutation/mosaicism would then depend on the location, timing and specific tissue in which the mutation occurred. It appears to now be appropriate to refer to all these conditions as "overgrowth" conditions, and sub-divide them further according to phenotypic presentation and tissue involved. This has already been done in the new IFSSH Classification of Congenital Anomalies, the OMT(Oberg Manske Tonkin) classification, where macrodactyly is placed into the general category of dysplasia, and then subdivided into hypertrophy or tumorous conditions, with further delineation depending on amount of upper limb involved.[4]

PIK3CA, along with mTOR and AKT, constitute a signaling pathway shown in Figure 3. This pathway is involved with the regulation of growth, protein synthesis and cellular proliferation. Mutations within this pathway have been found in various cancers, and treatment for the malignancies now is focused at blocking the mTOR receptors. This has led to the development of targeted chemotherapeutic agents with encouraging results in the cancer world.[5]

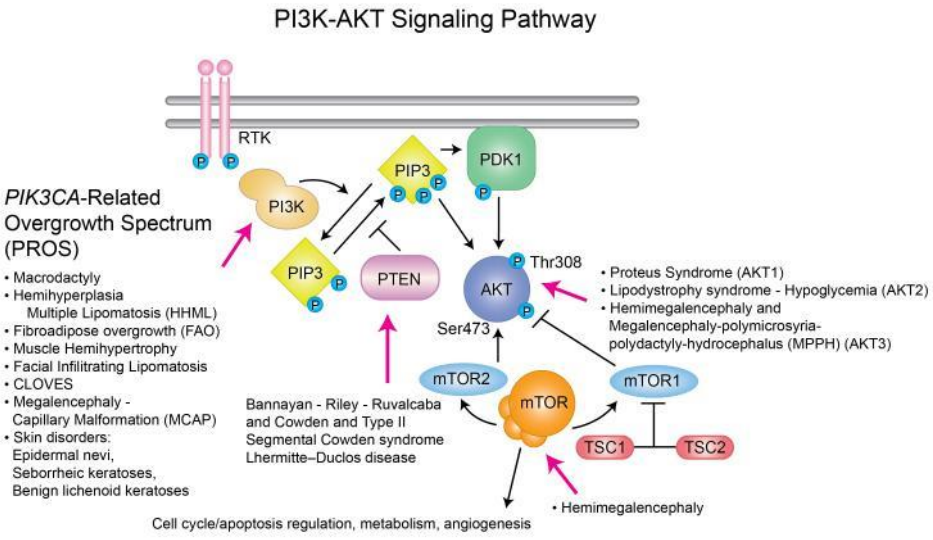

Figure 3. PI3K-AKT Pathway and associated clinical overgrowth disorders. Used with permission from Keppler-Noreuil et al. PIK3CA-Related Overgrowth Spectrum (PROS): Diagnostic and Testing Eligibility Criteria, Differential Diagnosis, and Evaluation. Am J Med Genet A. 2015 Feb; 0(2):287-295.

PROS conditions are non-malignant, although many have extensive associated morbidity (Figure 4A-D). It is hoped that the same mTOR blocking strategy used in cancer treatment can control or modulate the growth abnormality in children with PROS. Treatment will not reverse the condition, and must be administered over a prolonged period of time, with no clear endpoint.

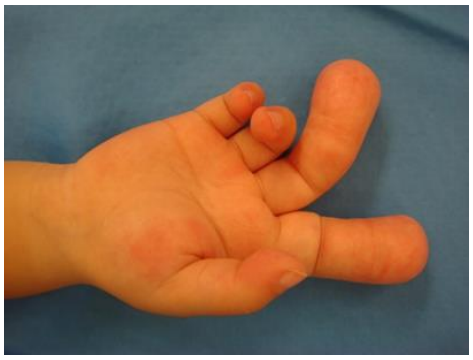

Figure 4A. PROS - macrodactyly

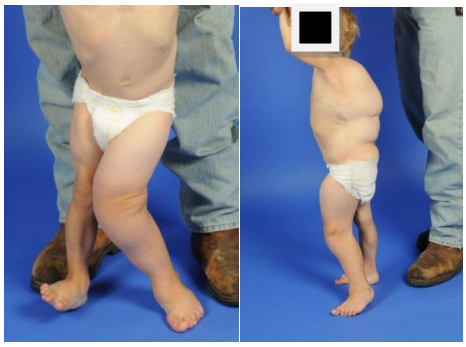

Figure 4B. PROS – CLOVES

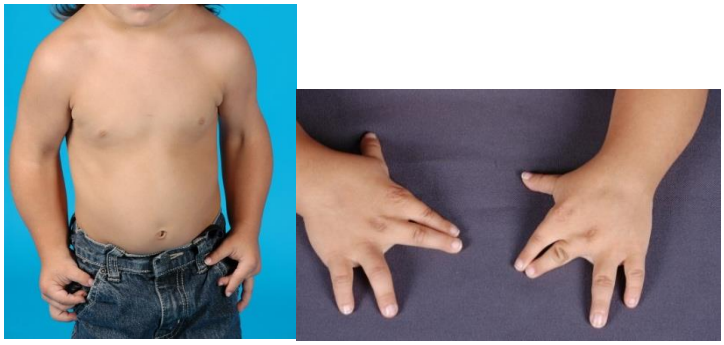

Figure 4C. PROS- Muscular Hemihypertrophy

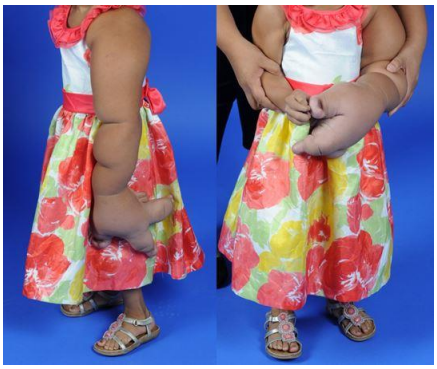

Figure 4D. PROS- Macrodystrophia Lipomatosa

Clinical trials have begun utilizing these medications to treat the most severe conditions, with promising results.[6,7] At our institution we have treated several patients with large vascular components with mTOR blocking agents, and have been likewise encouraged with the short-term results. However, at this time it is unclear exactly which patients can benefit from treatment. Side effects and morbidity include mucositis, hypercholesterolemia/hypertriglyceridemia, dyspnea, hypertension, anemia/ thrombocytopenia, peripheral edema, creatinine elevation, and potential hard tissue malignancy. Long-term follow-up is mandatory. In the next few years hopefully we will have more information regarding ideal candidates and length of treatment.

Surgical treatment of patients with upper limb macrodactyly includes options such as ray amputation, de-bulking procedures, and epiphysiodesis depending on the clinical findings. In patients with mild to moderate enlargement de-bulking +/- epiphysiodesis can be a reasonable option; however in patients with extremely large index and/or middle fingers with very little use ray amputation is a good alternative as multiple de-bulkings and epiphysiodeses procedures are unlikely to improve function or cosmetic appearance. (Figure 5) A recent publication by Gluck and Ezaki[8] has outlined a reasonable algorithm for the treatment of these patients. (Figure 6)

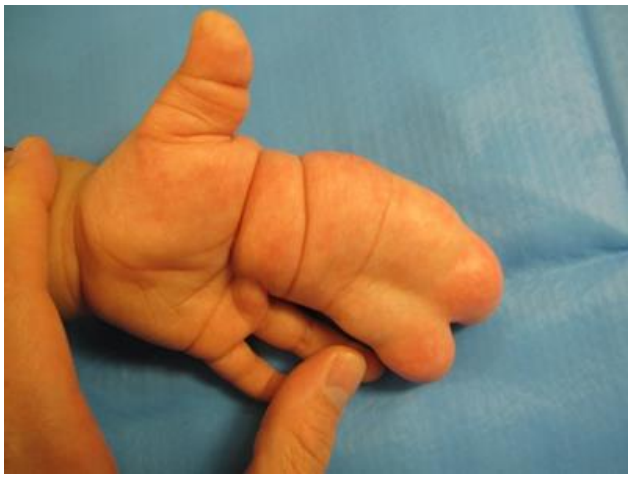

Figure 5.

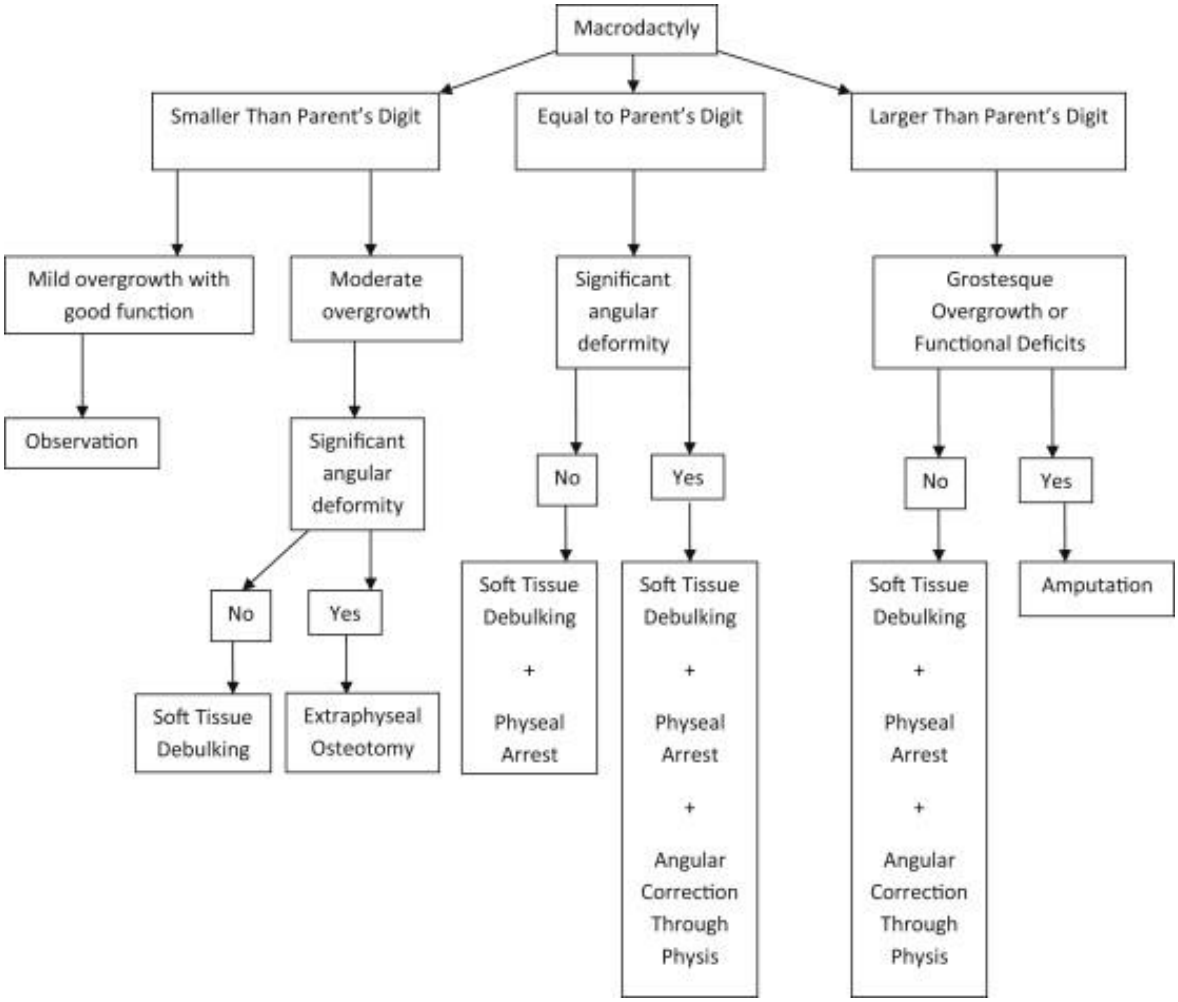

Figure 6. Treatment algorithm. Used with permission from Gluck J & Ezaki M. Surgical Treatment of Macrodactyly. J Hand Surg Am. 2015;40(7):1461-1468.

Summary

Somatic mutations resulting in limb overgrowth can present as macrodactyly alone or involve the whole upper or lower limb as well as many types of different tissue. DNA sequencing has identified mutations along the PI3K-AKT signaling pathway as the culprit in the affected tissue. Treatment can involve observation, surgery for de-bulking/ amputation, and/or chemotherapeutic agents for mTOR blockade. Hopefully in the near future we will be able to identify the appropriate time and place for each type of intervention.

References

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