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Crossed hemi-hyperplasia with hemi-megalencephaly – An unusual syndromic presentation

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SUMMARY

Hemimegalencephaly is a rare disorder which may present alone or be associated with hemicorporal gigantism. However, an association with crossed hemicorporal gigantism involving different upper and lower halves of the body along with selective visceromegaly is, so far, unreported in literature.

A 14-year-old male presented with a crossed variety of hemi-gigantism associated with a mild form of hemimegalencephaly affecting the left cerebral and cerebellar hemispheres. On ultrasound, left renomegaly was noted, though no pathology or dysfunction of the organ could be demonstrated.

This case merited a report due to an unusual presentation that defies explanations offered so far for the condition.

Key words: Hemimegalencephaly – Localized gigantism – Renomegaly

List of abbreviations:

HME (Hemimegalencephaly)
MDL (Macrodystrophia lipomatosa)
PROS (PIK3CA related overgrowth syndromes)

INTRODUCTION

The hormonal basis of gigantism and acromegaly has long been established and the etiology acceptable by virtue of its very logic. A localized manifestation of the disorder, however, cannot claim to be the result of the same causative factors given the omnipresence of circulating hormones. As Moore commented, the very definition of a hormone necessitates its accessibility and consequent effect on most body tissues (Moore, 1941).

Localized gigantism, though rare, is well documented in literature. Fischer (1880), as cited by Lassmann et al. (1977), attempted to distinguish primary (inborn) and secondary forms of localized gigantism, the former being rare and the latter a consequence of chronic venous congestion or lymphedema.

A report of a unique case is presented, in which a primary form of localized gigantism presented in an interesting pattern, affecting mesodermal and neuro-ectodermal derived tissues with no discernible effect on organs or tissues originating from the primitive endoderm.

CASE REPORT

A 14-year-old Indian male, offspring of non-consanguineous parents, presented with painless, asymptomatic enlargement of multiple segments of his anatomy (Figs. 1, 2). The patient's mother gave a history of an uneventful pregnancy terminating in

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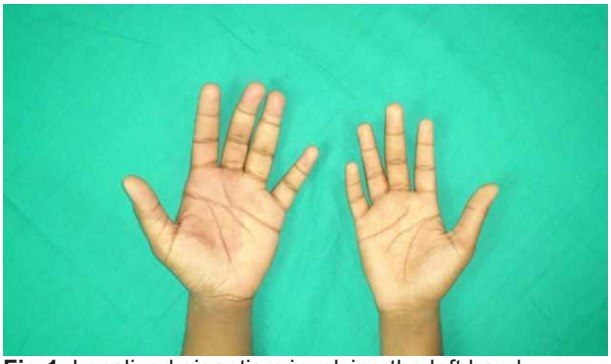

Fig 1. Localized gigantism involving the left hand.

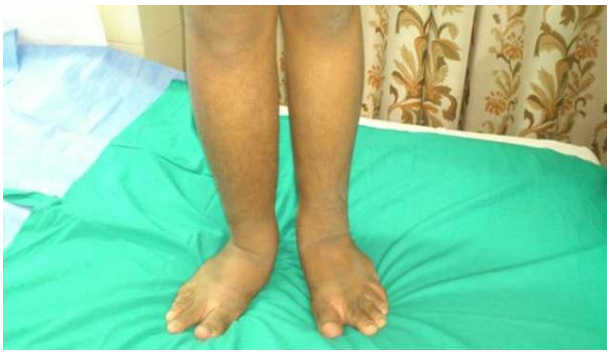

Fig 2. Gigantism involving the right lower limb with bilateral involvement of the feet.

a normal vaginal delivery.

The hypertrophied regions included soft tissue on the left side of the face, left sided maxilla and mandible, left upper limb involving all the bones and soft tissue and a similar presentation of the right lower limb. Bilateral involvement was noted only in case of the feet (Figs. 1, 2, 3).

Localized enlargement of parts of the child's body was first observed by the parents at around 6 months of age. Subsequent gradual progress of the same over the ensuing years was noted. Since the deformity was not gross or disabling in any fashion, the parents had not sought medical attention earlier. Their present approach was exclusively fueled by the patient's recent awareness and concern about his body image. There were no associated cutaneous manifestations such as café-au-lait spots, nodules, surface irregularities or localized asymmetry, port wine stains or freckling. No pitting edema, thrills, bruits or varicosities could be demonstrated. Examination of the eyes revealed no pathology of any kind. Dentitions, nails and hair were normal. Plain radiographs revealed a mild asymmetry of the left calvarium, as well as the left facial bones. No intra-cranial calcification was noted and the sella turcica appeared radiologically normal. Bony and soft tissue involvement of the affected limbs could be discerned. Joints were noted to be normal. However, consequent to unilateral involvement of the lower limb, a pelvic tilt was noted.

Head MRI showed the following findings (Fig.3):

- Thickening of the overlying bony calvarium with minimum scalloping of its inner table.
- T1 weighted axial image of cerebellum shows enlargement of left cerebellar hemisphere.
- T2 weighted axial image of brain at the level of lateral ventricles shows enlargement of left hemisphere with an attendant increase in the size of the ipsilateral lateral ventricle.
- T1 weighted coronal image of the face shows left sided hypertrophy of subcutaneous fat.
- T1 weighted axial image at the level of the mandible shows left sided mandibular enlargement.
- Muscles of the face and neck spaces showed normal morphology and signal intensity.

The MRI brain did not show any evidence of aneurysms, arterio-venous malformations or thrombosis. There was no evidence of focal irregularity or calcification. Grey and white matter distribution was normal.

- Post contrast studies did not reveal evidence of pial angiomatosis or gross enlargement of the left choroid plexus. Both parotid glands appeared normal in size, signal characteristics and enhancement patterns.

Ultrasonography revealed a left renal enlargement with a proportionate increase in the size of the calyceal system (Fig. 4). No obstructive pathology was noted and renal parenchyma appeared normal. No collateral renal pathology was noted clinically or revealed during routine investigations. All other organs were essentially normal. No involvement of lymphoid organs was noted. The pattern of involvement precluded the manifestation to be exclusive to a particular nerve territory. Skin over the affected area appeared completely normal in terms of surface characteristics, thickness, color and texture.

Oral glucose suppression test revealed growth hormone levels to be within normal limits. The leucocyte count and erythrocyte sedimentation rate were both well within the normal range.

The past medical history of the patient was unremarkable. The patient appeared to be of normal intellect with no learning disability. His milestones were normal. There was no history of convulsions. Neurological evaluation revealed nothing noteworthy.

There was no history of a similar nature or, for that matter, of any type of congenital abnormality in the immediate or extended family, as known to the parents.

DISCUSSION

Hemi-hypertrophy or hemi-hyperplasia is a presentation involving one half of the body with the overgrowth affecting either a solitary or several segments of the anatomy (Dalal et al., 2006,

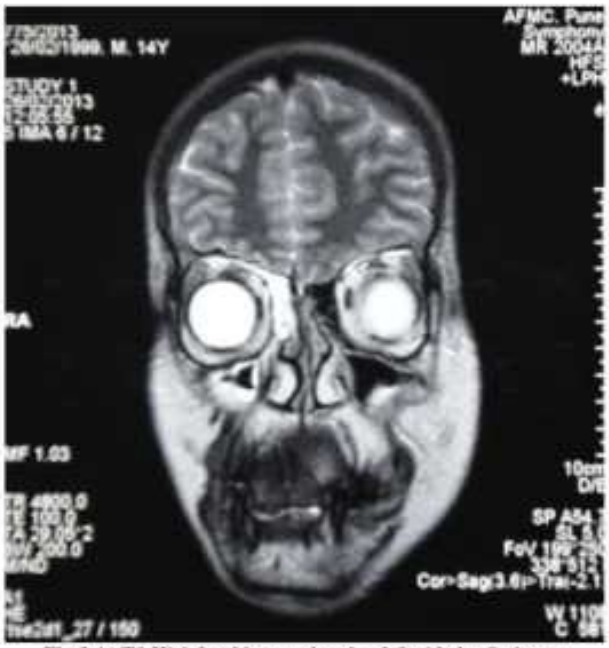

Fig.3 A) T1 Weighted image showing left sided soft tissue enlargement of the face along with bony enlargement of ipsilateral mandible and maxilla

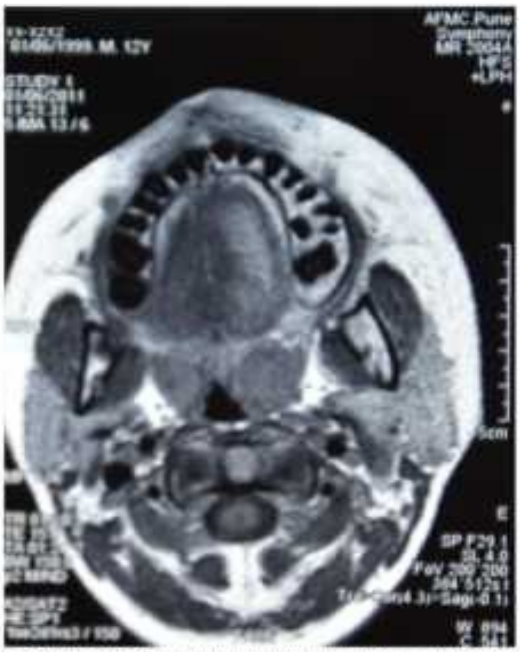

Fig.3 B)T1 Weighted image showing gross bony enlargement of left maxilla and palate along with soft tissue enlargement

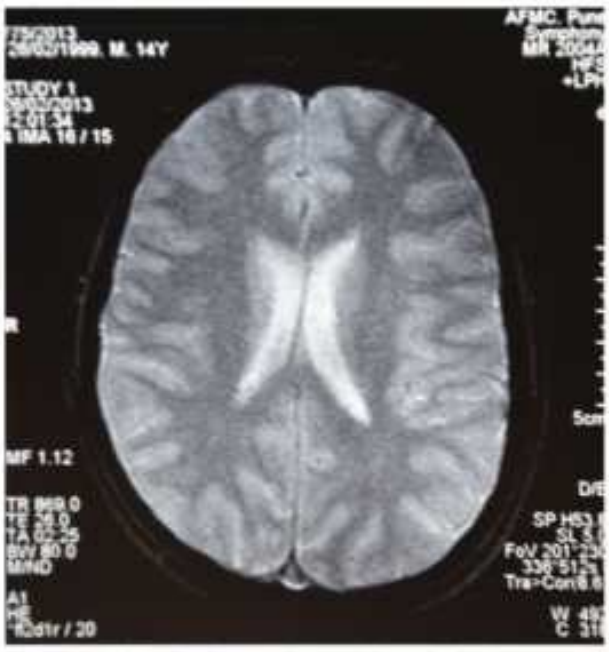

Fig.3 C)T2 Weighted image showing left cerebral enlargement with enlargement of the ipsilateral lateral ventricle

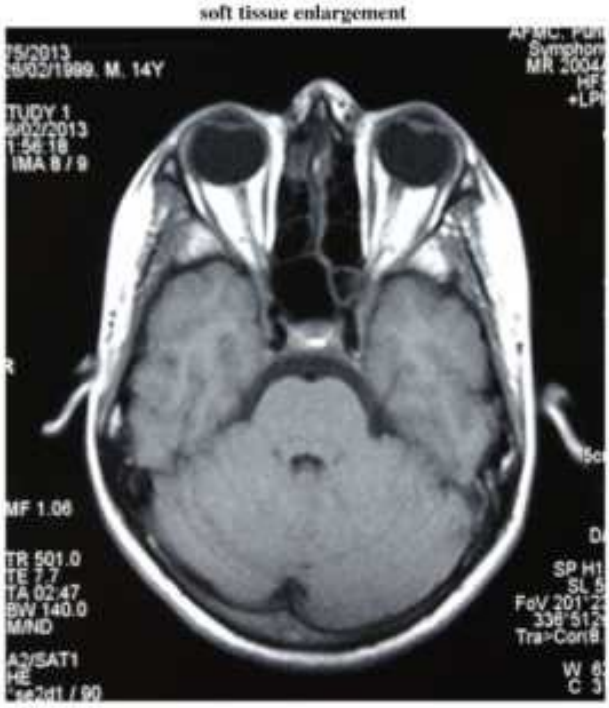

Fig.3 D)T1 Weighted image showing left cerebellar enlargement

Fig 3. A) T1 weighted image showing left sided soft tissue enlargement of the face along with bony enlargement of ipsilateral mandible and maxilla; **B**) T1 weighted image showing gross bony enlargement of left maxilla and palate along with soft tissue enlargement; **C**) T2 weighted image showing left cerebral enlargement with enlargement of the ipsilateral lateral ventricle; **D**) T1 weighted image showing left cerebellar enlargement.

Elawady and Ragab, 2017).

Crossed hemifacial hypertrophy involving facial asymmetry along with a co-existent enlargement of the opposite lower extremity, though rare, have been reported (Nayak and Baliga, 2007). To put it in perspective, Pollock et al. (1985), in their study of 192 cases of facial hemi hypertrophy, could find only five reported cases of crossed hyperplasia. The novelty of the present case included the alternating laterality of the affected tissues, the lack of involvement of all tissues within an affected area (dentition and musculature over the affected half of the face were normal) and the concurrent involvement of a kidney and nervous tissue.

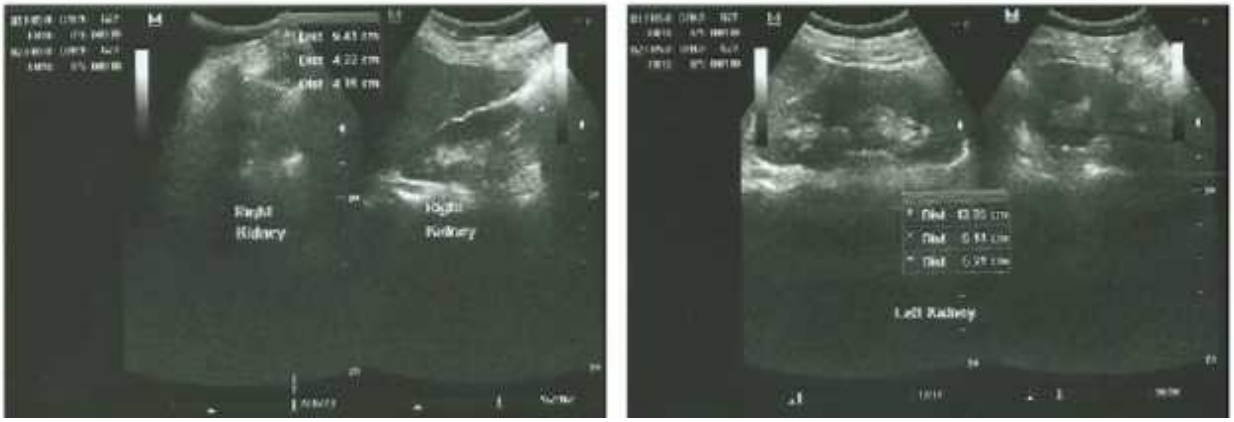

Fig 4. A) Ultra sonogram of the right kidney showing normal dimensions and cortical echo texture; **B**) Ultra sonogram of the left kidney showing enlarged kidney.

Localized gigantism includes a gamut of disorders which would need to be considered.

Macrodystrophia lipomatosa (MDL), thought to be a localized form of Proteus syndrome, typically involves nerve territories with proliferation of mesenchymal elements in the affected area and predisposition for distal involvement, including the phalanges and soft tissues of the digits (Goldman and Kaye, 1977). The condition involves an acapsular localized proliferation of fibro-fatty tissue producing a hamartomatous growth, which is typically asymmetrical and without involvement of other types of tissue (Kwon et al., 2013.). Lack of such a clinical picture in the present case where the enlargement was non-hamartomatous with an involvement of tissues other than just the fibro-fatty tissue ruled out the possibility of MDL. Moreover, unlike in MDL, the present case maintained lo ca l sym m e try a nd , a 'n o rma l' e xte rna l appearance of affected parts, except when compared with the size of the contralateral side.

Neurofibromatosis has well defined diagnostic criteria and may be suspected in case of neurocutaneous involvement, bilaterality and a positive family history (Singla et al., 2008).

Given the mosaic distribution, absence of positive family history and progressive course of the disorder, a mild variant of Proteus syndrome might have been a consideration but for the lack of any cutaneous or subcutaneous manifestation or lymphatic and vascular malformation, as shown by the MRI of the brain, head and neck.

Klippel-Trenaunay-Weber syndrome involves a localized hypertrophy, but necessarily includes cutaneous capillary malformations and varicose veins so as to form a triad of diagnostic features (Kihiczak et al., 2006). Lymphangiomas and hemangiomatosis were obviously not even considered probable diagnoses given the clinical picture.

Though isolated hemi-hyperplasia has also been associated with Wilm's tumor (Mutafoglu et al., 2010), it could not be applied to the present case as, despite the enlarged kidney, there was no pathology or malfunctioning of the organ noted.

The present case, by the very virtue of the absence of any noteworthy feature apart from a crossed hemi hypertrophy of neuro-ectodermal and mesodermal derived tissues and an interesting involvement of the left sided kidney made the above listed conditions unacceptable diagnoses.

Hemimegalencephaly (HME) per se is a rare, sporadic, non-familial congenital brain malformation (Terra-Bustamantec et al., 2006). The condition may be isolated or associated with ipsilateral hemicorporal hypertrophy (Terra-Bustamantec et al., 2006).

The likelihood of the presented case being a variant of HME was considered. The novelty, however, was the pattern of presentation which would not allow the case to conform to any of the defined prototypes of the disorder.

An association of macrosomia with nephromegaly can be noted in the Beckwith-Wiedemann syndrome complex, with a major presentation of the former while a minor one of the latter (Debaun et al., 2002). The present case somehow incorporates both these conditions, yet differs by virtue of the presence of megalencephaly and the crossed manner of hemi-gigantism.

Thus, the patient's manifestations, though mild, seemed to form a new syndrome complex, including megalencephaly, crossed hemicorporal gigantism and visceromegaly. Mosaic pattern of the phenotypic presentation in this patient indicates the pathophysiology involving exclusive cell sets, and thus would be necessarily a post-zygotic event. The fact that endodermal- and surface-ectodermal-derived tissues were completely exempted, as were many mesenchymal-derived cells and tissues, indicates the approximate age of the causative aberration being beyond the gastrula stage of the conceptus.

Pollock et al. (1985) have proposed an embryological hypothesis for hemifacial hypertrophy, in which they suggest that an asymmetrical development of the neural fold and subsequent hyper-

plasia of the ipsilateral neural crest cells would result in the anomalous condition. Although such an explanation would account for the presence of concomitant ipsilateral cerebral and cerebellar enlargement in the present case, it would fail to explain the appendicular and renal asymmetry. It is possible that, as a caudal extension of Pollock's hypothesis, further asymmetry included a unilateral incongruous buildup of somatopleuric and intermediate mesenchyme during gastrulation, resulting in the limb and renal enlargements.

Keppler-Noreuil et al. (2015) attempted to streamline a number of overgrowth disorders manifesting in a segmental or mosaic pattern due to somatic mutations in the PIK3CA gene; collectively called 'PIK3CA related overgrowth syndromes' (PROS). The conditions have distinct yet overlapping clinical features in which localized gigantism would be one of the presenting manifestations, and some of which may also include megalencephaly as a component. The activation of PIK3CA leads to the increased growth of the affected tissues (Santis et al., 2017). Though the present case does not fit into the defined parameters of PROS as outlined by Keppler-Noreuil et al. (2015), it is possible that a similar mutation in selective cells within the embryo resulted in the overgrowth pattern seen.

To the best of our knowledge, such a presentation, unique both in the manner of presenting features as well as the absence of collateral nervous and vascular pathologies, has not yet been reported. In view of the non-hamartomatous and symmetric proliferation of the tissues in affected regions and a crossed manner of presentation, surgical intervention for improvement of body image, as desired by the patient, was difficult to provide.

AUTHORS' CONTRIBUTION

Dr (Brig) Alok Sharma and Dr Namita Sharma researched the case, reviewed the literature and drafted the initial manuscript.

Dr Ashutosh Sharma identified the novel presentation of the patient, conducted the diagnostic tests, researched and presented the case, reviewed and approved the final manuscript submitted.

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