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Hemihypertrophy Spectrum

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Abstract

Background: Hemihypertrophy is a condition in which one side or part of the body is larger than the other. The asymmetry can range from mild to severe. It is important to establish a diagnosis because hemihypertrophy is associated with an increased risk for embryonal tumors, mainly Wilms tumor and hepatoblastoma.

Patients and Methods: This study presents ten Egyptian children with variable extent of congenital hemihypertrophy. It included 5 males and 5 females ranging in age from 2 months to 13 years. Abdomino-pelvic ultrasonography, echocardiography, brain MRI and radiological assessment of apparent and possibly hidden bone hypertrophy were performed to all cases.

Results: Cases were classified into Isolated hemihypertrophy (IH) (5 cases), part of overgrowth syndromes (3 cases) and hemihypertrophy with other malformations not fitting any of the known overgrowth syndromes (2 cases). IH cases were subclassified into simple hemihypertrophy (3 cases) and complex hemihypertrophy (2 cases). All cases were sporadic. None of our cases showed malignant transformation.

Conclusion: Hemihypertrophy may be isolated or associated with other congenital malformations. Most isolated cases are sporadic in inheritance with low recurrence risk. Screening for whole body systems is important to detect visceromegaly or other congenital anomalies. Follow up is essential to help in better diagnosis, counseling regarding the course of the disease and the recurrence risk and for early detection of malignancies. Molecular studies will help early diagnosis and distinguishing different hemihypertrophy syndromes

Keywords: Asymmetry; Hemihyperplasia; Hemihypertrophy; Overgrowth syndrome

Introduction

The asymmetric overgrowth, usually termed hemihypertrophy, is more accurately referred to as hemihyperplasia, since the pathology involves an abnormal proliferation of cells (hemihyperplasia), not an increase in size of existing cells (hemihypertrophy) [1]. The asymmetry can be due to differences in the growth of soft tissue, bone, or both [2] Hemihyperplasia may be an isolated finding, or it may be part of multiple malformation syndromes, such as Russell-Silver syndrome, Proteus syndrome, Beckwith-Wiedemann Syndrome (BWS), and Sotos syndrome [3,4]. Isolated hemihyperplasia (IH, OMIM 235000) is defined as asymmetric regional body overgrowth due to an underlying abnormality of cell proliferation without any other underlying diagnosis [5]. Rowe [6] proposed a classification system for hemihyperplasia, based on anatomic site of involvement. According to this classification, complex hemihyperplasia is defined as involvement of half of the body (at least one leg and one arm), simple hemihyperplasia is the involvement of a single limb and hemifacial hyperplasia is the involvement of one side of the face. The etiology of IH is unknown. A number of different chromosomal anomalies, including trisomy [7] mosaicism and diploid-triploid mosaicism, have been identified, and the causes of IH are likely to be heterogeneous [5]. It has been suggested that IH could be one end of the spectrum of phenotypes of BWS [8], linked to the chromosomal locus 11p15 [9]. BWS is frequently recognizable because of characteristic features as hemihypertrophy, macroglossia, omphalocele, and organomegaly. The most common molecular cause is hypomethylation of the maternal imprinting control region 2 (ICR2) in 11p15.

Somatic activating mutations in the phosphatidylinositol-3-kinase/AKT/mTOR pathway underlie different segmental overgrowth phenotypes. Historically, the clinical diagnoses in patients with PIK3CA activating mutations have included Hemihyperplasia Multiple Lipomatosis (HHML), Vascular Malformations, Scoliosis/Skeletal and Spinal (CLOVES) syndrome, macrodactyly and the related megalencephaly syndromes, Megalencephaly-Capillary Malformation Polymicrogyria (MCAP or M-CM) and Dysplastic Megalencephaly (DMEG) [10].

MCAP is characterized by primary megalencephaly, prenatal overgrowth, brain and body asymmetry, digital anomalies consisting of syndactyly with or without postaxial polydactyly, cutaneous vascular malformations, connective tissue dysplasia involving the skin, joints and subcutaneous tissue, and cortical brain malformations, most commonly polymicrogyria [11,12]. This disorder is also known as the macrocephaly-capillary malformation (MCM) syndrome [13]. Mirzaa, et al. [14] suggested the use of the term MCAP rather than MCM to reflect the very large brain size, not simply large head size that characterizes this syndrome. Russell-Silver syndrome is a disorder present at birth that involves, low birth weight, poor growth, short stature, and body asymmetry. Characteristic features include triangular face, pointed, small chin and thin mouth [15].

Edmondson and Kalish [16] have reported elevated risk of neoplasm development in overgrowth disorders. Increased risk of embryonal tumors in cases with IH, is documented in case reports and prospective study by Hoyme et al [5]. They followed 168 children with IH for 10 years and reported 10 tumors in 9 cases including

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	Patient1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age	2 y	2 m	6 m	9 m	6 y	13 y	1 y	7 m	4 m	3 m
Sex	M	F	F	F	M	M	M	F	M	F
Consanguinity	no	no	no	no	no	yes	No	yes	yes	yes
Prenatal insults	no	no	Yes Electric shock and fainting	no	no	no	No	Yes Progesterone injections	no	no
Hypertrophy site	Rt cheek (face)	Face, Lower limbs	Rt. Upper& Lower limbs	Lt.arm	All Toes	Lt. Middle finger	Lt. 2nd, 3rd, 4th toes	Rt. hand Lower limbs	Rt. Upper & lower limbs	Skull , Rt.leg
Skin pigmentation	Facial hemangioma (Rt cheek, skin over Rt. mandible, Rt shoulder, lt. forehead and cheek)	Extensive hema.	no	Hema. of Lt.arm & shoulder	Café aulait patches on lt.hypochondrial & iliac regions	Café au lait patches on Rt hypochondrial and l\Lt scapular regions	Hypopig-mented area on anterior aspect of Lt. thigh	Small hema. on forehead	no	Hema. on lower back of head
Other malformation	Bil. glaucoma	Polydactyly of toes. Hemimegalencephaly	Dysmorphic Bil. Simian creases	no	Syndactyly of Rt. Toes. Undescended testis	no	no	no	no	Triangular face, pointed chin
Developmental Milestones	Delayed	Delayed	Delayed	N	N	N	N	N	N	N
Seizures	yes	yes	no	no	no	no	no	no	no	no
Brain CT/ MRI	Lt cerebral hemiatrophy	Lt.cerebral hemimegalencephaly &schizencephaly	Dilated ventricles	Normal	Normal	Normal	_	N	_	N
Other investigations	EEG: Lt hypoactive record	Echo, Abd U/S : N	Echo: ASD Abd. U/S: N	Echo, Abd U/S: N	Abd. U/S: undesended testis	Echo, Abd U/S: N	Abd U/S: N	Karyotype, Echo, Abd U/S: N	Abd U/S: N	Abd U/S: malrotated ectopic Lt kidney
Diagnosis	Sturge Weber syndrome (Hemifacial hypertrophy)	Megalencephaly Capillary Malformation Syndrome	?Syndromic (+ASD, Dysmorphism)	Simple Hemihyertrophy	?Syndromic (+ undescended testis, syndactyly)	Simple Hemihyertrophy	Simple Hemihyertrophy	Complex Hemihypertrophy	Complex Hemihypertrophy	Russell Silver syndrome

y=year, M=male, F=female, Rt=right, Lt=left, Hema.=Hemangioma, Bil.=Bilateral, N=Normal, ASD=Atrial septal defect U/S=Ultrasound, EEG=Electroencephalogram, Echo=Echocardiography

Table 1: History, clinical description and imaging data of cases with hemihypertrophy in this study.

Wilms tumors (WTs), adrenal cell carcinomas, hepatoblastoma (HBL), and small bowel leiomyosarcoma, giving a tumor incidence of 5.9%. Clericuzio, et al. [17] described five children (two with IH and three with BWS) for whom serial serum alpha-fetoprotein screening and abdominal ultrasound, led to early detection of HBL. Tan, et al. [18] have recommended measuring serum alpha-fetoprotein (AFP) every 3 months until age 4, by which time 90% of HBL will have developed. Caution in interpretation of infant AFP levels is important, as high levels of AFP is present at birth which fall rapidly to the normal adult level by 10-12 months of age [19,20].

Patients and Methods

The present study comprised ten Egyptian children with congenital hemihyperplasia. They consisted of 5 males and 5 females ranging in age from 2 months to 13 years. All patients were selected from among patients attending the outpatient Genetics clinic, Faculty of medicine, Fayoum University, Egypt, over a period of twenty-three months starting October 2013 through August 2015. Informed consent had been signed by all studied patients and their guardians according to the guidelines of the Medical Research Ethics Committee at Fayoum University. Enrolled cases were subjected to complete prenatal, personal and family histories with pedigree construction and full clinical examination. Abdomino-pelvic ultrasonography, echocardiography, brain MRI and radiological assessment of apparent and possibly hidden bone hyperplasia were performed to all cases.

Results

Ten cases were presented with variable extent of hemihyperplasia Table 1. Positive consanguinity was present in 5 cases (50%) (Figure 1). None of our cases had similarly affected family members. Prenatal histories were relevant in two cases (20%). One case had a history of maternal electric shock exposure at 5th gestational months and the other case had prenatal history of progesterone hormonal preparations intake from the second gestational month to the end of pregnancy. Eight cases (80%) had associated cutaneous lesions at different sites of their bodies. Two cases (20%) had dysmorphic features; (case no.2: depressed nasal bridge, hypertelorism, prominent forehead and bilateral simian creases; and case no 10: Triangular face, micrognathia and clinodactyly of little fingers) (Figure 2). Two cases (20%) had associated limb anomalies; case no 2 had right post axial polydactyly of toes; and case no 5 had partial soft tissue syndactyly between second and third toes of right foot. Three cases (no 1, 2 and 3) (30%) had delayed milestones of development out of which two cases had history of seizures. One case (no 3) (10%) had atrial septal defect with mild pericardial effusion (Figure 3). One case (no 10) (10%) had associated malrotated ectopic left kidney. One case (no 5) (10%) had undescended left testis. Case no 2 met the criteria of MCM syndrome and another case with hemifacial hyperplasia was diagnosed as SWS. Case no 10 (Figure 4) was diagnosed as Silver Russell syndrome. Two cases had complex hemihyperplasia in association with other malformation; which did not meet any of the known overgrowth syndromes. IH was diagnosed in five cases (50%) whom according to the proposed calcification of Rowe [6], were subclassified into simple hemihyperplasia (three cases 30%) and complex hemihyperplasia (two cases 20%). Follow up visits of our patients showed no sonographic findings of malignancy. In an attempt of cosmetic surgical correction, one case with isolated macrodactyly of left middle finger had an operation to reduce its size but unfortunately it increased in size later.

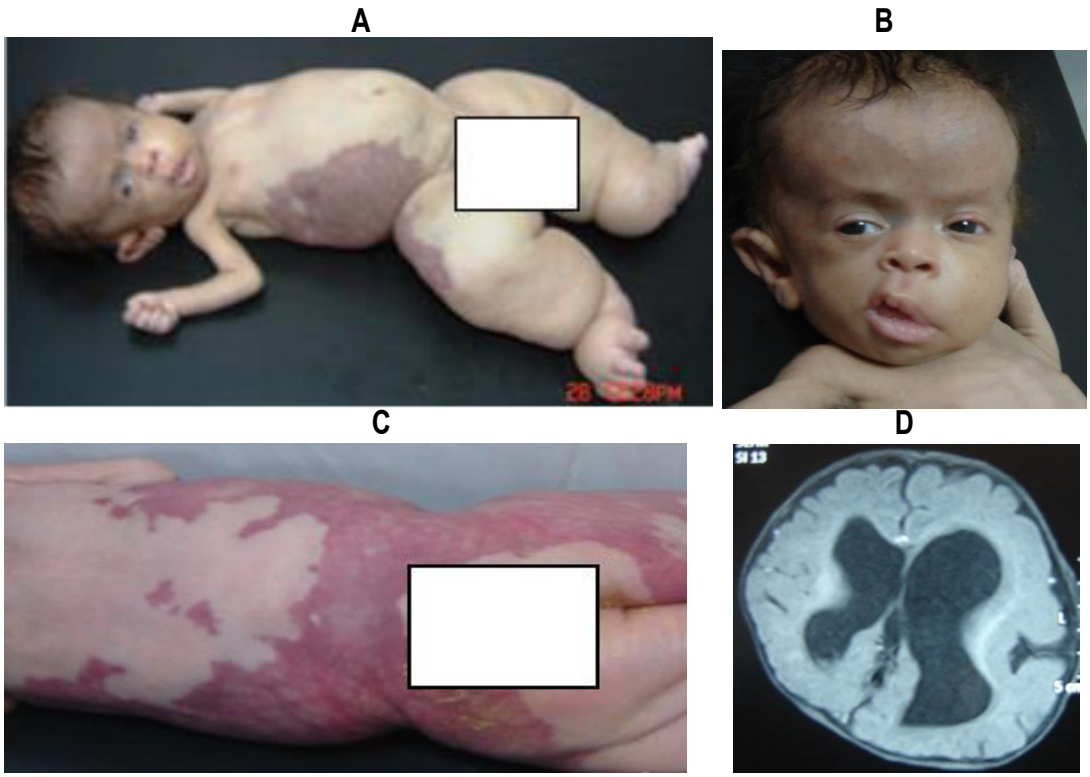

Figure 1: (A) Patient no 2: A 2-month old female with Megalencephaly capillary malformation syndrome; (B) The facial asymmetry ; (C) lower limbs hypertrophy, extensive hemangioma; (D) Brain MRI showed left hemimegalencephaly, closed lip schizencephaly and periventricular band of heterotopia.

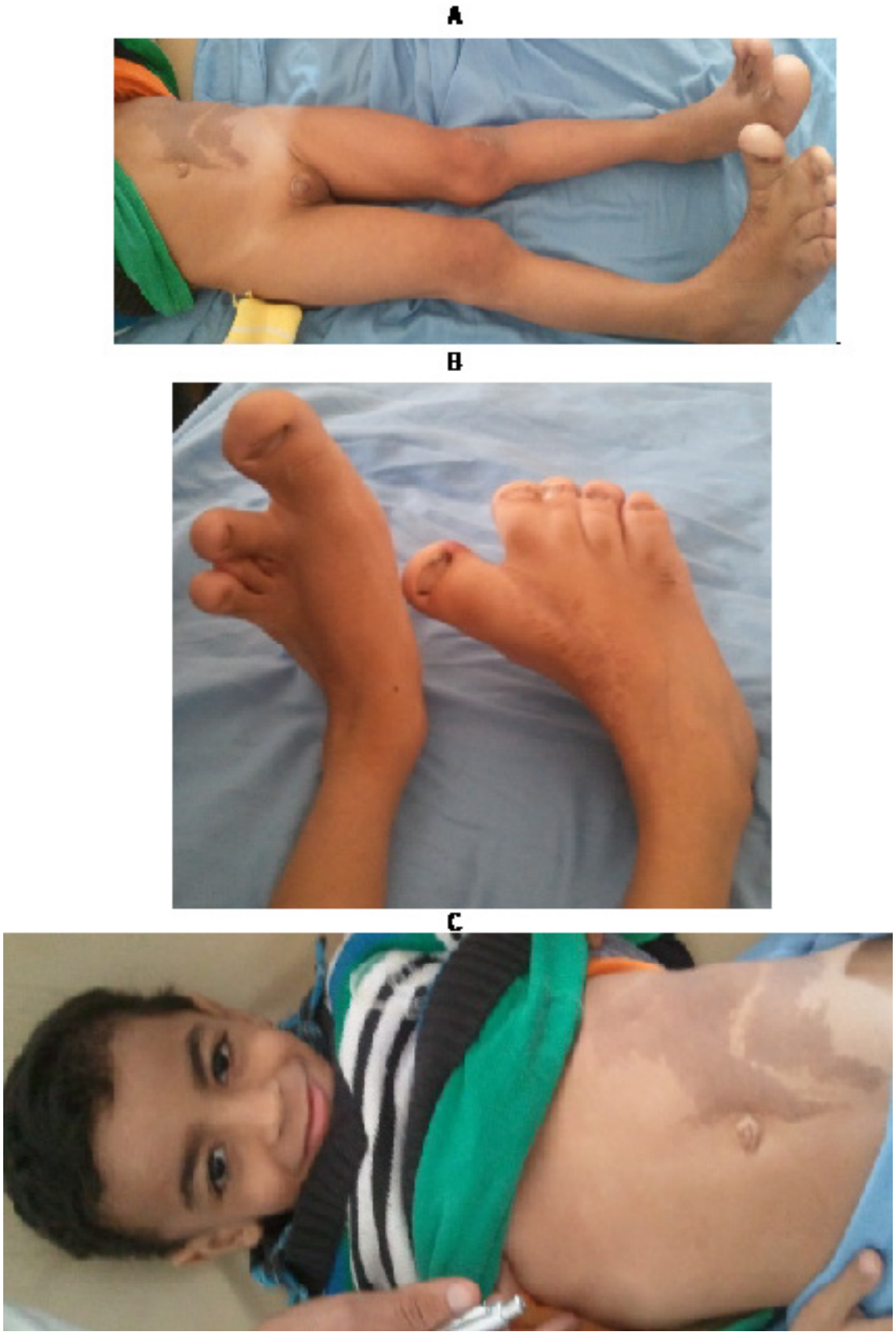

Figure 2: (A) Patient no. 5: A 6-year old boy with bilateral megalodactyly of toes; (B) partial soft tissue syndactyly between right 2nd and 3rd toes; (C) Café aulait patches. Pelviabdominal sonar showed left undescended testis.

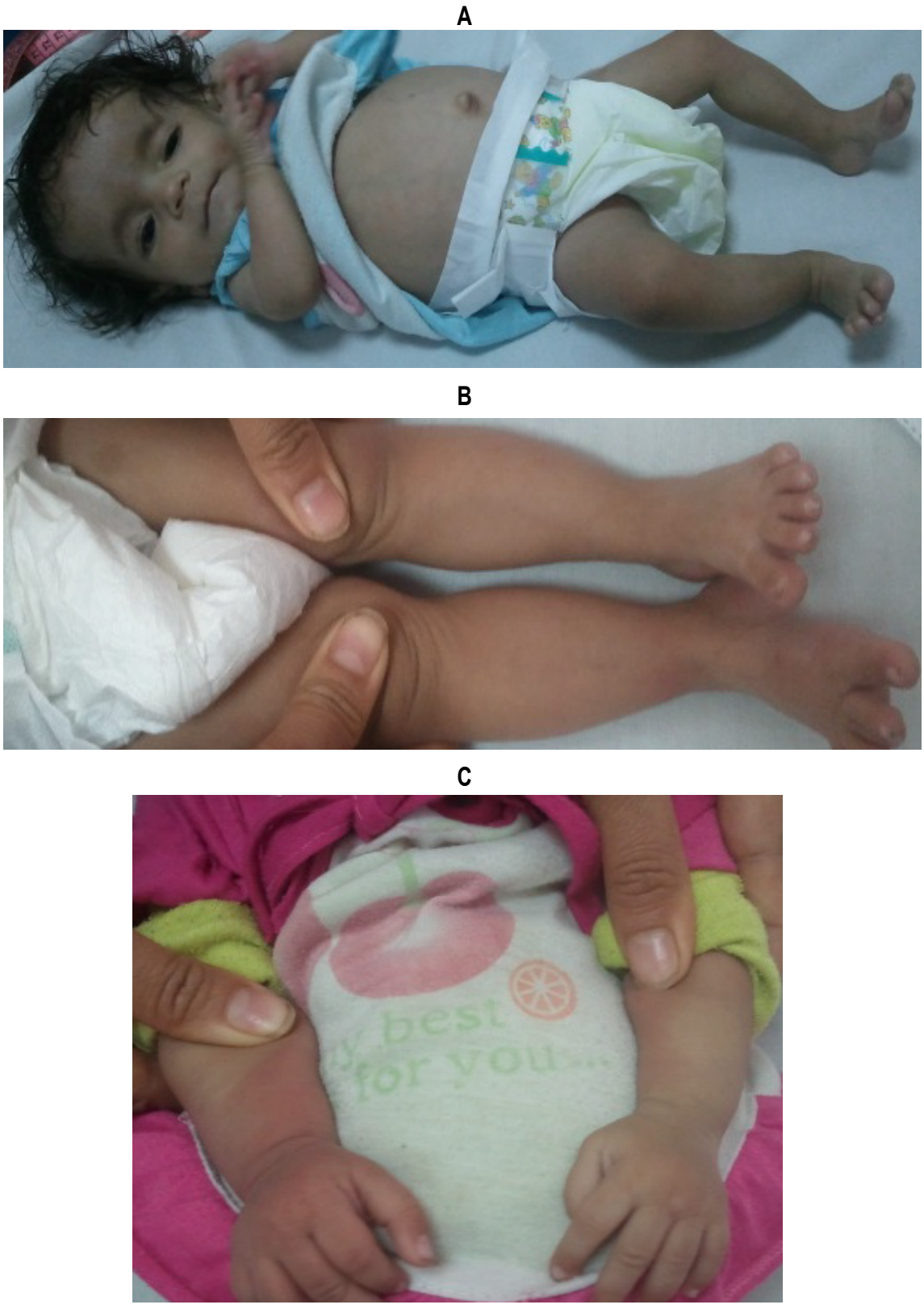

Figure 3: (A) Patient no.10: 3-month old female child with hemihypertrophy of right side of skull and right lower limb. The right lower limb is thicker and longer compared to the left side; (B) There is hemangioma on the back of the skull; (C) Features suggestive of Russell Silver syndrome

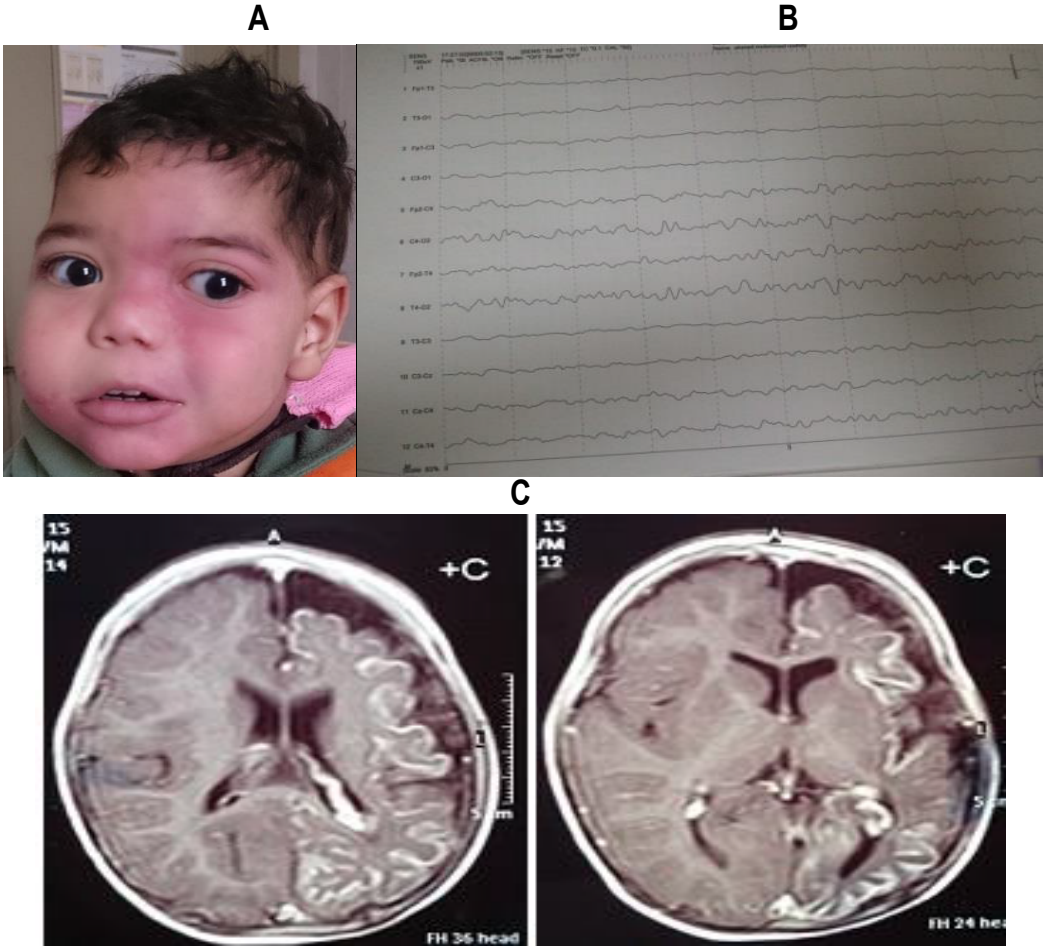

Figure 4: (A) Patient no 1: 2 years old child diagnosed as Sturge Weber syndrome. There is associated right hemifacial hypertrophy. Congenital hemangioma affecting skin over right cheek, mandible and extends to right shoulder; (B) The child had delayed motor and mental milestones and bilateral congenital glaucoma.; (C) Brain CT showed reduce volume of left cerebral hemisphere with prominent leptomeningeal enhancement and enlarged ipsilateral choroid plexus. EEG showed left side hypoactivity.

Discussion

Hemihyperplasia, is a condition in which there may be asymmetrical overgrowth of the face, cranium, trunk, and/or limbs on one side of the body [21,22]. There may be asymmetrical visceromegaly on the ipsilateral or contralateral side [9]. The incidence of IH is ~1/86 000 live births, [7,23] with a male: female ratio of 1:2 [22] . In the current study, all cases were sporadic and had negative family history with male to female ratio of 1:1. Isolated hemihyperplasia is usually sporadic with low recurrence risk. Barsky [24] and others found no report of familial occurrence. On the other hand, there have been many reports of familial hemihyperplasia in the literature with two or more affected relatives [24-32]. However, some of these patients had additional features, suggesting that not all of the families had IH [27]. In this study, we had five cases (50%) with IH; all were sporadic with no similar affected relatives. Three cases with IH had history of positive consanguinity.

Lacombe and Battin [26] described 2 children diagnosed at birth as isolated megalodactyly. Their follow-up examination showed development of hemihypertrophy and other findings suggesting Proteus syndrome [9]. However, our case (case no 6) had isolated megalodactyly of right middle finger. Megalodactyly was present since birth and had increased in length and thickness over time without involvement of other parts or organs. The child had three oval café au lait patches on right hypochondrium and two on left scapular region. Greene, et al. [32] stated that facial hypertrophy is a major component of SWS; and patients should be counseled for the risk of overgrowth and for the types of possible surgical correction. However, hemifacial hyperplasia maybe also present as isolated malformation. Deshingkar, et al. [30] reported a mentally healthy 12-year old boy with isolated hemifacial hypertrophy. The patient's face was asymmetrical with an enlargement of the right side, including the maxillary, malar, and mandibular region. Our case of SWS (case no. 1) is a 2-year old male child with history of global developmental delay and seizures. He has hemifacial hypertrophy of the right side, including the malar, maxillary and mandibular regions. Similarly, Babaji, et al. [33] presented a case of SWS with osseous hypertrophy of maxilla.

Kumar, et al. [34] presented a 15-year-old boy with Silver-Russell syndrome. He was well-appearing, thin, and short with normal head circumference. Asymmetry of his hands, phalanges, and lower extremities were noted, with hemihypertrophy of the left lower extremity. Similarly, our case (case no 10) is a 3-month old girl with typical features suggestive of Silver-Russell syndrome [35,36] . She has hypertrophy of right side of the skull and her right lower limb is longer and thicker than her left lower limb. Follow up visits showed

the discrepancy of limbs size and length and the skull asymmetry. She had poor weight gain and short stature but she had within normal milestones of development. On Review of literature, case no. 2 had features suggestive of MCAP (OMIM # 602501) overlapping with megalencephaly, polymicrogyria-polydactyly hydrocephalus syndrome (MPPH; OMIM, 603387). These features are congenital macrocephaly, cranium and face asymmetry, bilateral lower limbs hyperplasia, right post axial polydactyly of toes, massive body hemangioma with brain MRI showing hemimegalencephaly of left cerebral hemisphere with closed lip schizencephaly, periventricular band like heterotopia and areas of lissencephaly. Mirzaa, et al. [12] reviewed the phenotypic features of 42 patients with a megalencephalic syndrome in a trial to clarify and simplify the classification and diagnosis of these disorders. Statistical analysis of particular features yielded 2 major groups: 21 patients with a vascular malformation consistent with MCAP and 19 with no vascular malformation consistent with MPPH; 2 patients were in an overlap group. Vascular malformations were associated with syndactyly and somatic overgrowth at birth, and lack of vascular malformations was associated with polydactyly. The different features were assigned to 5 major classes of developmental malformations. Both MCAP and MPPH had (1) megalencephaly and different somatic overgrowth (specially in MCAP); (2) distal limb malformations, polydactyly being more associated with MPPH and syndactyly with MCAP and (3) similar cortical brain malformations (mostly polymicrogyria). In addition, MCAP included (4) Vascular abnormalities and (5) occasional connective tissue dysplasia, such as thick skin or hyperelasticity. MPPH lacks connective tissue dysplasia, vascular malformations, and heterotopia. Based on these findings, Mirzaa, et al. [12] proposed diagnostic criteria for MPPH and MCAP syndromes, and postulated that the 2 malformations represent different, although overlapping, syndromes that possibly caused by different genes involved in the same biologic pathway. Our case had right postaxial polydactyly of toes which is more common in MPPH, in association with vascular malformations and left cerebral hemisphere megalencephaly with heterotopia which are mainly features of MCAP.

Conclusion

Hemihyperplasia/hemihypertrophy has an extremely variable presentation. It may be isolated or part of a syndrome. Most isolated cases are sporadic in inheritance with low recurrence risk. Many syndromes with hemihyperplasia are well recognized. Screening for whole body systems is important to detect visceromegaly or other congenital anomalies or malignancies. Follow up is essential to help in better diagnosis, counseling regarding the course of the disease and the recurrence risk and for early detection of malignancies. Molecular studies will help early diagnosis and distinguishing different hemihypertrophy syndromes to predict other associated malformations for early and better management.

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