International Journal of Contemporary Pediatrics
Shetty D et al. Int J Contemp Pediatr. 2023 Apr;10(4):563-567
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20230738

Case Series

Congenital hand anomalies and rare syndromes in children

Deepa Shetty[1]*, Paras Patel[1], Rohan Shetty[3], Sanjay Vansh[2]

[1]Department of Pediatrics, [2]Department of ENT, ESIC Model Hospital, Vapi, Gujarat, India
[3]Department of ENT, ESIC, MHB, Ahmedabad, Gujarat, India

Received: 13 February 2023
Revised: 10 March 2023
Accepted: 14 March 2023

***Correspondence:**
Dr. Deepa Shetty,
E-mail: shettydeepa200@gmail.com

ABSTRACT

Congenital hand anomalies and associated rare syndromes in children are commonly seen in clinical practice and require complete clinical, radiological and genetic evaluation. The purpose of this case series is to describe four rare syndromic children with varied hand anomalies and differences. Three of the children are female and one is a male. Distal limb defects from simple polydactyly, clinodactyly to cleft hand were identified including preaxial anomalies. Significant clinical problems noted were chiefly cosmetic and altered self-image was also noted in one child. The orofacial clefting noted in the child with ectrodactyly ectodermal dysplasia (EEC) syndrome required repeated surgery though the child had minimal feeding difficulty and significant speech delay. Multidisciplinary management is necessary with the early involvement of clinical geneticist.

Keywords: Polydactyly, Ectrodactyly, Ectodermal dysplasia, Cleft palate, Amniotic band syndrome, Childhood obesity

INTRODUCTION

Children presenting to the speciality outpatient department are clinically evaluated and screened for multiple anomalies and associations which are uncommon yet not so rare in common clinical practice. For a paediatric specialist the diagnostic challenge lies in asking the positive family history, history of consanguineous marriage, birth history and complete clinical examination with relevant investigations in a busy district hospital with limited resources. Managing the patient and family as a whole and a multidisciplinary approach with involvement of the geneticist are newer and wholesome treatment and management approaches. Any congenital hand anomaly can become a hindrance for the child to attain his or her maximum potential. Hand deformities can be particularly disabling as the child learns to use his or her limbs to appreciate and reciprocate with the environment. There are specific types of congenital hand differences few of which are described in this case series. There could be minor deformities like uneven, unequal fingers, fused digits or absent thumb or major defects like absent bone. Early consultation for reconstructive surgery as well as functional prosthetics play a very important and life changing role in early rehabilitation.[1]

CASE SERIES

The first case is of a 4-year-old boy who presented to our outpatient department with short stature and preaxial polydactyly and when he was evaluated further he had an incidental finding of horseshoe kidney and thrombocytopenia. He is under regular follow up with hematologists and nephrologists and is diagnosed to have thrombocytopenia absent radius (TAR) syndrome (Figure 1).

The second child is a 4-year-old girl operated on cleft lip and palate which had partially corrected however needing revision surgery who presented with no family history of

any such deformity (Figure 2). The examination of the upper extremities was remarkable for ectrodactyly with the right hand showing clefting and absence of first three digits and thumb. The lower extremities were normal. The scalp hair and eyebrows were light, short, thin, brittle and kinky (Figure 3). The child's skin was significantly thickened and dry especially on the extremities. Opthalmological examination revealed epiphora. Audiometric analysis showed no conduction blockade. Considering the clinical signs and symptoms a provisional diagnosis of ectrodactyly-ectodermal dysplasia clefting syndrome (EEC) was made.

Figure 1: Right preaxial polydactyly in a 4-year-old with short stature.

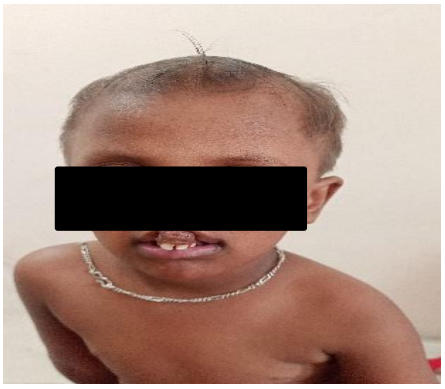

Figure 2: 4-year-old girl with operated cleft lip and palate and sparse.

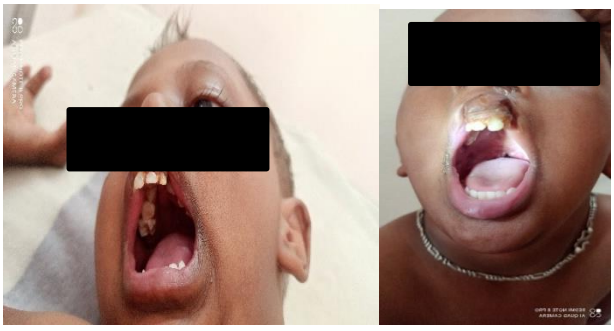

Figure 3: Partially corrected cleft lip and palate and ankyloblepharon and right hand ectrodactyly and clefting.

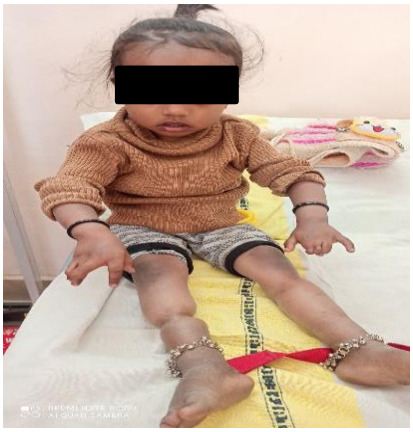

Figure 4: 3-year-old with amniotic band syndrome, partially amputed digits and constriction band around right lower limb.

The last case is a 10-year-old girl with no family history of obesity who has a body mass index above the 99th centile presenting with obesity and acanthosis nigricans with short fourth and fifth digits in both hands and widely spaced digits of feet (Figures 5 and 6). She is diagnosed to have metabolic syndrome and phenotypic features suggesting Bardet-Biedl syndrome however she needs a further genetic evaluation to confirm the diagnosis (Figure 6).

Figure 6: Knuckle knuckle dimple dimple sign in an obese girl with acanthosis nigricans.

DISCUSSION

The currently accepted groups of classifying hand deformities are as follows; problems in formation of the parts, failure of the parts of hand to separate, duplications of fingers, undergrowth of fingers, overgrowth of fingers, congenital constriction band syndrome and other generalized problems with the skeletal system.[1] Thrombocytopenia absent radius syndrome and other

syndromes like Fanconi anemia and Noonan syndrome are associated with hand anomalies. Upper extremity abnormalities associated with TAR syndrome as in our first case in the case series range from isolated absent radii to phocomelia. Abnormalities include bilateral radial aplasia, radial club hand, hypoplastic carpals and phalanges, hypoplastic ulnae, humeri and shoulder girdles, syndactyly and clinodactyly of fingers and toes, selective hypoplasia of middle phalanx, fifth digit, altered palmar contours.[2] Previous studies done have shown how the length of the upper limb can affect the patients functional ability.[3] They divided upper-limb defects into 3 categories of severity as follows; the first group (71%) had mild defects consisting of radial aplasia with various degrees of ulnar and humeral hypoplasia. The patients had normal shoulder girth and near-normal upper-body strength but splints were still useful for periods of prolonged activity of the upper limbs. The second group (18%) had increased degrees of limb shortening, humeral hypoplasia and underdevelopment of the shoulder girth with decreased upper-body strength. Splints were also useful in this group. The last group was the most affected with severe ulnar and humeral shortening and phocomelia. Lower extremity anomalies occur in 46% of patients and vary from clinically undetectable changes to phocomelia. These anomalies are usually less severe than those of the upper limbs. Abnormalities include hip dislocation, femoral torsion, tibial torsion, valgus and varus foot deformities, deformity of the knee (e.g. absence of the patella, patellar dislocation), absent tibiofibular joint, abnormal toe placement, fifth toe overlapping the fourth. In distinguishing TAR from other syndromes involving skeletal abnormalities of the upper extremities, the following features may be of assistance. Patients with TAR syndrome always have thumbs but thumbs are usually absent or hypoplastic in children with Fanconi anemia and radial defects. Fanconi anemia is also associated with chromosomal fragility, a rare onset of thrombocytopenia before age 1 year and pancytopenia in children aged 5-10 years. A reliable diagnostic test is a chromosomal breakage study. Thumb abnormalities include absent, hypoplastic and triphalangeal thumbs in Holt-Oram syndrome and blood counts are normal. The patient often has a family history of heart and limb defects due to the autosomal dominant pattern of inheritance. Thrombocytopenia is not often observed in Roberts syndrome (Roberts-SC phocomelia). Most patients with this syndrome have microcephaly and mental retardation. Radial hypoplasia is found in patients with Aase syndrome, but the thumb is triphalangeal. Hypoplastic anemia is the usual presentation similar to that of Blackfan-Diamond syndrome. Thrombocytopenia is not a feature. TAR syndrome was initially considered an autosomal recessive disease. Some have suggested that the inheritance pattern may be autosomal dominant with variable penetrance. The HOX family of genes plays a major role in embryogenesis and cell differentiation, including differentiation of hematopoietic cell lines. However, Fleischman and colleagues did not detect mutations in the coding sequence of HOX genes known to affect radial development.[4] Subsequently an interstitial microdeletion of chromosome 1q was identified in 30 patients with TAR syndrome.[5] All patients and 75% of unaffected parents in this cohort had the microdeletion, suggesting co-inheritance of an additional modifier gene for disease expression. Albers and colleagues applied high-through put sequencing in 5 unrelated patients with TAR syndrome and the chromosome 1q21.1 deletion.[6] They discovered one low frequency single nucleotide polymorphism(SNP) in the noncoding 5' untranslated (UTR) region of the gene RBM8A in 4 of the cases and another low frequency non coding SNP in the first intron of the same gene. These findings were further confirmed in 48 individuals with TAR syndrome. The investigators found coinheritance of the 1q21.1 deletion with either SNP, causing significant decreases in the level of Y 14, a protein encoded by RBM8A.[7] The exact mechanism for which decreased levels of Y14 produces the phenotype associated with TAR syndrome remains to be elucidated. Y14 is part of the exon-junction complex (EJC), a set of proteins associated with transcript export, localisation and splicing, playing a critical in embryonic development.[8,9] Some studies have suggested defects in signal transduction downstream of thrombopoietin. In the second case the differential diagnosis considered was Hay-Wells syndrome (Ankyloblepharon ectodermal dysplasia).[10] EEC syndrome is a genetic developmental disorder featuring ectrodactyly, ectodermaldyplasia and facial clefts may also be noticed with characteristics like recurrent urinary tract infections, vesicoureteral reflux, photophobia, anomalies of kidney, hearing loss and speech defects.[11] Although it is an autosomal dominant condition, some cases occur sporadically without previous history of the disorder (i.e. new-mutations).[12] The present case could be a sporadic one as there was no previous history of the disorder in the family. Ectrodactyly involves the absence of one or more central digits of the hand or foot giving rise to claw-like appearance.[10] Many sporadic cases of EEC syndrome have been reported. Ectrodactyly with tetramelic 3-4 syndactyly results in the characteristic lobster-claw deformity of the hands and feet.[13] Hypoplastic metacarpal or metatarsal bones may be present. Cleft lip and palate create a characteristic nasal contour. Other ectodermal anomalies include mild hypohydrosis; coarse dry hair with hypotrichosis; xerostomia; dystrophic nails, dental enamel hypoplasia and microdontia. Associated defects include blepharophimosis, lacrimal duct anomalies, strabismus, deafness, choanal atresia and abnormalities of the genitourinary tract. The 3 most commonly recognized ectodermal dysplasia: ectrodactyly and clefting (EEC) syndrome; Hay-Wells syndrome or ankyloblepharon, ectodermal dysplasia and cleft lip/palate (AEC) syndrome; and Rapp-Hodgkin syndrome, all of which are caused by mutations in the TP63 gene.[14] Although some ectodermal dysplasia syndromes with an identifiable genetic basis is increasing. In 2009,64 genes and 3 chromosomal loci were associated with 62 ectodermal dysplasias.[11] Key transcription factors and intracellular signalling pathways that have been implicated in the ectodermal dysplasias include the tumor necrosis

factor (TNF)-like/TNV receptor signalling pathway which involves ectodysplasin (EDA), the EDR receptor (EDAR), the EDAR-associated death domain (EDARADD); the WN5 signaling pathway; the NF-Kb essential signally pathway, which involves the NF-Kb essential modulator (NEMO); and the transcription factor p63.[15] Ectodermal dysplasia results from the abnormal development of embryonic ectodermal structures. The genetic defects responsible for approximately 30 of the ectodermal dysplasias have been identified. However, a detailed understanding of the pathophysiology underlying most forms of ectodermal dysplasia with regards to the mechanisms by which the underlying genetic defects impact the growth and development of ectodermal structures is lacking. The management of this child is multidisciplinary and is directed towards the specific signs and symptoms, including pediatrician, pediatric surgeon, plastic surgeon, orthopaedic surgeon, orthopedists, dentist, speech therapist and other health professionals.

The third case is a condition known as amniotic band syndrome.[16] This syndrome is also known as ADAM complex, amniotic band sequence, Streeter's dysplasia, congenital constriction bands and pseudoainhum.[16] It is a sporadic condition and does not appear to be genetic or hereditary. They may be associated with other congenital anomalies such as syndactyly, clubfoot, cleft palate and cleft lip and can also present with severe craniofacial and visceral deformities. The antenatal diagnosis may be difficult however a prenatal radiodiagnosis can help indirectly showing swelling of digits or limbs distal to the constriction.[17]

Children born with amniotic band syndrome are usually full-term or a few weeks premature.[18]Although the condition is quite variable in presentation the most common clinical findings in ABS appear on the extremities and include amputation followed by constriction bands and then acrosyndactyly. On the extremities the distal portion is most often involved, especially the longer central digits of the hand (middle, long and index fingers). The hands are affected in almost 90% of cases.[19] If the compression from the band is severe, lymphatic and vascular compromise mat ensue and the child presents at birth with a swollen engorged digit or limb that may require immediate surgical release.[20] Extremity deformities in ABS are commonly classified into Patterson's four types as follows. Type I-simple ring constriction; type II-ring constriction accompanied by fusion of the distal bony parts with or without lymphedema; type III-ring constrictions accompanied by fusion of soft-tissue parts; and type IV-intrauterine amputations.[18] Treatment mostly occurs after birth but with advancement of prenatal radiodiagnosis, fetal surgery in utero has been tried.[21]

Plastic and reconstructive surgery and orthopaedic surgery planning and timing of repair are important to provide improved function and development while providing a more acceptable aesthetic appearance.[22] Long term physiotherapy and occupational therapy should continue. Clinically significant limb-length discrepancy may also be present and patients need to be sequentially monitored even after correction of bands. These conditions may lead to limited function and difficulty with ambulation.[23-25] Because ABS is an intrauterine phenomenon probably caused by the rupture of amniotic membranes and constriction of the developing tissue, no medical treatment exists for the condition. Indications for intervention depend on the medical stability of the child and on the neurovascular status of the limb. Limb defects are known to be associated with Laurence Moon Bardet-Biedl syndrome which is a syndrome associated with pediatric obesity. In an original study short, broad, stubby fingers and toes were reported in 51 patients (46%).[26] In many the thumb was placed proximally, there was fifth finger clinodactyly or there was a prominent sandal gap between the first and second toes. Nine patients (8%) showed syndactyly this was usually partial, most commonly involving the second and third toes. Complex influences operate on limb differentiation despite an identical genotype and a similar intrauterine environment as seen by previous studies done on twins.[26] The diagnosis remains difficult in young patients as clinical findings develop later in adult life. Appropriate genetic counselling for families and adequate medical follow-up for affected children is required for effective disease management.[27]

CONCLUSION

Early diagnosis will help parents to get accurate care and rehabilitation including genetic counselling. Genetic counselling will benefit the affected children and their families. Future genetic research should be emphasized to identify the loci contributing to the syndromes like EEC and to differentiate it from other syndromes and to help in diagnosis and treatment plan. Specific treatment for congenital hand deformities will be determined by the child's age, overall health and medical history extent of the condition, cause of the condition, child's tolerance for specific medications, procedures or therapies and expectations for the course of the condition. Treatment may include limb manipulation and stretching, splinting of the affected limbs, tendon transfers, external appliances (to help realign misshapen fingers or hands), physical therapy (to help increase the strength and function of the hand), correction of contractures, skin grafts which involve replacing or attaching skin to a part of the hand that is missing skin or has been removed during a procedure. Prosthetics may be used when surgery is not an option, or in addition to surgical correction.

ACKNOWLEDGEMENTS

Authors would like to acknowledge all parents and their children who consented to share their clinical photographs.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Congenital Hand Deformities/Johns Hopkins Medicine. Health. Available at: https://www.hopkins medicine.org/health. Accessed on 06 January 2023.
2. Wu JK, Williams S. Thrombocytopenia-Absent Radius Syndrome. Hematologic Disorders. Rare Diseases. Diseases and Conditions. Medscape. Available at: https://emedicine.medscape.com/ article/959 262 - overview?src=mbl_msp_android& ref=share. Accessed on 06 January 2023.
3. Greenhalgh KL, Howell RT, Bottani A, Ancliff PJ, Brunner HG, Verschuuren-Bemelmans CC, et al. Thrombocytopenia-absent radius syndrome: a clinical genetic study. J Med Genet. 2002;39(12):876-81.
4. Fleischman RA, Letestu R, Mi X, Stevens D, Winters J, Debili N, et al. Absence of mutations in the HoxA10, HoxA11 and HoxD11 nucleotide coding sequences in thrombocytopenia with absent radius syndrome. Br J Haematol. 2002;116(2):367-75.
5. Klopocki E, Schulze H, Strauss G, Ott CE, Hall J, Trotier F, et al. Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. Am J Hum Genet. 2007;80(2):232-40.
6. Albers CA, Newbury-Ecob R, Ouwehand WH, Ghevaertc. New insights into the genetic basis of TAR (thrombocytopenia -absent radii) syndrome. Curr Opin Genet Dev. 2013;23(3):316-23.
7. Albers CA, Paul DS, Schulze H, Freson K, Stephens JC, Smethurst PA. Compound inheritance of a low-frequency regulatory SNP and rare null mutation in exon-junction complex subunit RBM8A causes TAR syndrome. Nat Genet. 2012;44(4):435-9.
8. Le Hir H, Gatfield D, Izaurralde E, Moore MJ. The exon-exon junction complex provides a binding platform for factors involved in mRNA export and non-sense-mediated mRNAdecay. EMBO J. 2001;20(17):4987-97.
9. Le Hir H, Izaurralde E, Maquat LE, Moore MJ. The spliceosome deposits multiple proteins 20-24 nucleotides upstream of mRNAexon -exon junctions EMBO J. 2000;19(24):6860-9.
10. Kaul M, Dwivedi R, Upadhyay V. Ectrodactyly-ectodermal dysplasiaclefting syndrome (EEC syndrome). J Oral Biol Craniofac Res. 2014;4(2):135-9.
11. Visinoni AF, Lisboa-Costa T, Pagnan NA, Chautard-Freire-Maia EA. Ectodermal dysplasias: Clinical and molecular review. Am J Med Genet A. 2009;149A(9):1980-2002.
12. Sabhlok S, Mishra S, Tripathy R, Mony D. Ectrodactyly ectodermal dysplasia-cleft lip/palate syndrome: a rare entity. Plastic Aesthetic Res.2015;2(1):290-3.
13. Shah KN. Ectodermal Dysplasia. 2019. Pediatric Diseases. Rare Diseases. Diseases & Conditions. Medscape. Available at: https://emedicine.medscape. com/article/1110595-overview?src=mbl_msp_ android&ref=share. Accessed on 06 January 2023.
14. Okamura E, Suda N, Baba Y, Fukuoka H, Ogawa T, Ohkuma M, et al. Dental and maxillofacial characteristics in six Japanese individuals with ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome. Cleft Palate Craniofac J. 2012;11.
15. Priolo M. Ectodermal dysplasias: an overview and update of clinical and molecular-functional mechanisms. Am J Med Genet A. 2009;149(9):2003-13.
16. Shetty P, Menezes LT, Tauro LF, Diddigi KA. Amniotic band syndrome. Indian J Surg. 2013;75(5):401-2.
17. Tadmor OP, Kreisberg GA, Achiron R, Porat S, Yagel S. Limb amputation in amniotic band syndrome: serial ultrasonographic and Doppler observations. Ultrasound Obstet Gynecol. 1997;10:312-5.
18. Do TT. Amniotic Band Syndrome (Streeter Dysplasia). 2020. Pediatrics. Orthopedic Surgery. Diseases & Conditions. Medscape. Available at: https://emedicine.medscape.com/article/1260337-overview?src=mbl_msp_android& ref=share. Accessed on 06 January 2023.
19. Light TR. Growth and development of the hand. Carter PR, editor. Reconstruction of the Child's Hand. Philadelphia: Lea & Febiger. 1991;122.
20. Iba K, Wada T, Yamashita T. Pre-operative findings of acrosyndactyly and sharpening of distal portion of the phalanx related to post-operative fingertip pain in constriction band syndrome. J Hand Surg Eur. 2012;37(3):287-8.
21. Soldado F, Aguirre M, Peiro JL, Carreras E, Arevalo S, Fontecha CG, et al. Fetoscopic release of extremity amniotic bands with risk of amputation. J Pediatr Orthop. 2009;29:290-3.
22. Kawamura K, Chung KC. Constriction band syndrome Hand Clin. 2009;25:257-64.
23. Iqbal CW, Derderian SC, Cheng V, Lee H, Hirose S. Amniotic band syndrome: a single-institutional experience. Fetal Diagn Ther. 2015;37(1):1-5.
24. López-Muňoz E, Becerra-Solano LE. An update on amniotic bands sequence. Arch Argent Pediatr. 2018;116(3):e409-20.
25. Hennigan SP, Kuo KN. Resistant talipes equinovarus associated with congenital constriction band syndrome. J Pediatr Orthop. 2000;20(2):240-5.
26. Beales PL, Elciogler N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl Syndrome: results of a population survey. J Med Genet.1999;36(6):437-46.
27. Sathya P, Sheela N, Parveen S, Sripriya S. Bardet-Biedl syndrome: Genetics, molecular pathophysiology and disease management. Indian J Opthalmol. 2016;64(9):620-7.

Cite this article as: Shetty D, Patel P, Shetty R, Vansh S. Congenital hand anomalies and rare syndromes in children. Int J Contemp Pediatr 2023;10:563-7.