

CASE REPORT

Congenital isolated Iso–Kikuchi syndrome in a newborn

Enrico Valerio¹, Francesca Favot², Ilaria Mattei² & Mario Cutrone²

¹Department of Woman and Child Health, Neonatal Intensive Care Unit, Medical School, University of Padua, Padova, Italy

²Department of Pediatrics, Pediatric Dermatology Unit, Ospedale Dell'Angelo, Mestre (VE), Italy

Correspondence

Enrico Valerio, Department of Woman and Child Health, Medical School, University of Padua, Via Giustiniani, 3, 35128 Padova, Italy. Tel: +39 0498213545; Fax: +39 0498213301; E-mails: enrico.valerio.md@gmail.com, enrico.va@inwind.it

Funding Information

No sources of funding were declared for this study.

Received: 19 March 2015; Revised: 14 June 2015; Accepted: 6 August 2015

Clinical Case Reports 2015; 3(10): 866–869

doi: 10.1002/ccr3.367

Key Clinical Message

Classic CO (also called Iso–Kikuchi syndrome) represents a benign, isolated condition associated with normal patient outcome. Nevertheless, clinical follow-up and/or further clinically-based tests are needed to exclude other nail diseases associated with multisystem pathology; complete family history is also important to determine sporadic or hereditary transmission of such condition.

Keywords

Anonychia, dermatology, Iso–Kikuchi syndrome, newborn, onychodysplasia.

Case Report

A healthy newborn was delivered vaginally at 39+6 weeks' gestation. Pregnancy course was regular, except for maternal consumption of mebendazol at 5 weeks' gestation to treat a pinworm infection. Maternal history was negative for consumption of any known teratogenic class drug during the whole pregnancy.

Clinical examination at birth was normal, except for complete congenital anonychia of left middle finger (Fig. 1).

X-ray was performed, showing an absence of the left middle finger distal phalanx (Fig. 2). The rest of the nails on the fingers and toes were normal. Parents were not consanguineous and have normal fingernails and toenails. The baby was discharged on the third day of life, and was found healthy and thriving at three-month follow-up visit. Final diagnosis was that of a sporadic CO.

Discussion

Congenital onychodystrophy (CO), also called as Iso–Kikuchi syndrome, was first described by Iso in 1969 [1]

and later by Kikuchi in 1974 [2] as a clinical syndrome involving dysplasia/absence of fingernails with underlying bone abnormalities.

Since these first observations, clinical criteria have been expanded to include a number of additional associated conditions derived from small series, case reports, and retrospective reviews over the next 30 years. CO clinical criteria are the following:

- unilateral or bilateral hypoplasia of the index fingernails and/or other fingers including toenails [3] (up to total anonychia of hands and feet);
- radiographic abnormalities of the distal bony phalanx of the affected fingers;
- congenital occurrence, which can be both sporadic or hereditary [4, 5].

When inherited, transmission pattern of this condition seems to be autosomal dominant [6]. Genetic loci responsible for the condition are still under investigation: linkage to the known keratin gene clusters on 12q12 and 17q21 has been excluded by Kresova et al. in 2000; [7] a putative isolated congenital nail dysplasia locus, designated NDIC, has been identified on 17p13, although the



Figure 1. Congenital isolated anonychia of the left middle finger.



Figure 2. X-ray showing absence of left middle finger distal phalanx.

identified region harbors no genes known to be involved in skin or nail abnormalities [7].

Several *acquired* isolated nail disorders which may represent differential diagnoses of CO are presented in Table 1 [8]. Differently from all these conditions, CO presents as a *congenital* hypoplasia, dysplasia, or absence of one or more fingernails, and is typically accompanied by underlying phalanx bone disease.

Several heterogeneous multisystem pathologies may also come with ungueal abnormalities; these are summarized in Table 2 [8–13].

Table 1. Acquired isolated nail disorders [8].

Condition name	Nail disorder description	Notes
Onychomatricoma	Localized or diffused thickening of the nail plate, yellow discoloration, holes in the nail plate free edge	Benign neoplasm of the nail matrix
Onychopapilloma	Monodactylous longitudinal erythronychia, leukonychia, or melanonychia, often with presence of a keratotic notch under the distal nail plate	Possibly related to human papillomavirus (HPV) infection
Nail lichen striatus	Lichenoid nail changes limited to the medial or lateral side of the nail plate	Self-limited linear dermatosis of unknown etiology

Differently from the above-mentioned conditions, classic CO does not come with involvement of systems other than nails and relative phalanges.

Pathogenesis of this benign condition is still poorly understood. Kikuchi originally suggested fetal grip as a causative mechanism of nail and phalanx ischemia, leading to dysplasia or even complete resorption of such structures [14]. This theory, however, is not consistent with the recent acquisitions on developmental biology stating that limbs and bones develop early in fetal life, prior to fetus' ability to exert a significant grip.

More recently, several pathogenetic mechanisms have been proposed for this condition:

- selective abnormal fetal vascular supply from palmar digital artery causing *in utero* ischemic injury: the ischemic damage would mainly be seen on the radial side of the affected finger due to the smaller caliber of the artery on that side [15], which should be more protected than the ulnar one; [16]
- *in utero* dysplastic change in the crescent-shaped cap of the distal phalanx, a theory that would account for the frequent “Y” shape of the dysplastic distal phalanx, when present; [17]
- genetic mutations causing impairment of the WNT signaling pathway, an evolutionarily conserved signal transduction pathway that plays a pivotal role in embryonic development, growth regulation of multiple tissues, and cancer development; [18]
- fetal exposure to teratogens, particularly antiepileptic drugs: phenytoin [19], valproate, and carbamazepine [20]

A literature research showed no proven association between the use of mebendazole during pregnancy and

Table 2. Multisystem pathologies associated to ungueal abnormalities [8–13].

Condition name	Nail disorder description	Additional features	Notes
Nail–patella syndrome	<ul style="list-style-type: none"> • Triangular nail lunula • Fingernails and toenails hypoplasia [8] 	<ul style="list-style-type: none"> • Absent or hypoplastic patellae • Elbow dysplasia, often involving posterior subluxation of the radial head • Iliac horns dysplasia 	The condition reflects dysplasia of structures derived from the dorsal mesenchyme[9]
Hypohidrotic/Anhidrotic ectodermal dysplasias	Fingernails dysplasia	Classical triad: [10] <ul style="list-style-type: none"> • Hypodontia • Hypotrichosis • Hypohidrosis 	Group of X-linked inherited disorders characterized by dysplasia of tissues of ectodermal origin
Anonychia-lymphedema	<ul style="list-style-type: none"> • Arrested or reduced nail growth • Thickened and over-curved nails with absence of cuticle 	Diffused lymphedema and pleural effusion [11, 12]	Also called “Yellow nail syndrome”
Onychodystrophy–deafness syndrome	Nail dystrophy (up to complete anonychia)[13]	Congenital sensorineural hearing loss	Lysosomal acidification defect

CO. Conversely, helminth infection during pregnancy is associated with poor cognitive and gross motor outcomes in infants, so that measures to prevent helminth infection during pregnancy should be reinforced;[21] anthelmintic therapy is actually recommended in infected pregnant women, and it has been associated to a decreased rate of maternal anemia and low birth weight [22].

Conclusions and final remarks

Classic isolated CO represents a benign condition associated with normal neurodevelopmental outcome. Nevertheless, clinical follow-up is needed in order to exclude other conditions associated with multisystem pathology; a complete family history may also be warranted to determine sporadic or hereditary transmission of such a condition.

Conflict of interest

None declared.

References

1. Iso, R. 1969. [Congenital nail defects of the index finger and reconstructive surgery]. *Seikei Geka*. 20:1383–1384.
2. Kikuchi, I., S. Horikawa, and F. Amano. 1974. Congenital onychodysplasia of the index fingers. *Arch. Dermatol.* 110:743–746.
3. Biedermann, T., C. G. Schirren, H. Schirren, and C. A. Sander. 1995. [Congenital onychodysplasia (Iso-Kikuchi syndrome)]. *Hautarzt* 46:53–56.
4. Nevin, N. C., P. S. Thomas, D. J. Eedy, and C. Shepherd. 1995. Anonychia and absence/hypoplasia of distal phalanges (Cooks syndrome): report of a second family. *J. Med. Genet.* 32:638–641.
5. Afsar, F. S., and A. Karakuzu. 2014. Total congenital anonychia. *Pediatr. Dermatol.* 31:743–744.
6. Hamm, H., S. Karl, and E.-B. Brocker. 2000. Isolated congenital nail dysplasia: a new autosomal dominant condition. *Arch. Derm.* 136:1239–1243.
7. Krebsova, A., H. Hamm, S. Karl, A. Reis, and H. C. Hennies. 2000. Assignment of the gene for a new hereditary nail disorder, isolated congenital nail dysplasia, to chromosome 17p13. *J. Invest. Derm.* 115:664–667.
8. Schneider, S. L., and A. Tosti. 2015. Tips to Diagnose Uncommon Nail Disorders. *Dermatol. Clin.* 33:197–205.
9. Sweeney, E., A. Fryer, R. Mountford, A. Green, and I. McIntosh. 2003. Nail patella syndrome: a review of the phenotype aided by developmental biology. *J. Med. Genet.* 40:153–162.
10. Shanbhag, V. K. 2015. Hypohidrotic ectodermal dysplasia. *Indian Dermatol Online J.* 6:136–137.
11. Hausmann, M., and R. Keller 1994. [Yellow nail syndrome]. *Pneumologie* 48:30–33.
12. Emerson, P. A. 1966. Yellow nails, lymphoedema, and pleural effusions. *Thorax* 21:247–253.
13. Yuan, Y., J. Zhang, Q. Chang, J. Zeng, F. Xin, J. Wang, et al. 2014. De novo mutation in ATP6V1B2 impairs lysosome acidification and causes dominant deafness-onychodystrophy syndrome. *Cell Res.* 24:1370–1373.
14. Kikuchi, I., S. Inoue, and N. Kawana. 1985. Congenital onychodysplasia of the index fingers. An abnormal grip theory. *J. Dermatol.* 12:258–262.

15. Edwards, E. A. 1960. Organization of the small arteries of the hand and digits. *Am. J. Surg.* 99:837–846.
16. Franceschini, P., D. Licata, A. Guala, G. Di Cara, and D. Franceschini. 2001. Peculiar facial appearance and generalized brachydactyly in a patient with congenital onychodysplasia of the index fingers (Iso-Kikuchi syndrome). *Am. J. Med. Genet.* 98:330–335.
17. Miura, T., and R. Nakamura. 1990. Congenital onychodysplasia of the index fingers. *J Hand Surg* 15: 793–797.
18. Bergmann, C., J. Senderek, D. Anhof, C. T. Thiel, A. B. Ekici, P. Poblete-Gutierrez, et al. 2006. Mutations in the gene encoding the Wnt-signaling component R-spondin 4 (RSPO4) cause autosomal recessive anonychia. *Am. J. Hum. Genet.* 79:1105–1109.
19. Babu, S., and N. Agarwal. 2012. Anonychia due to prenatal phenytoin exposure. *J. Assoc. Physicians India* 60:64.
20. Eadie, M. J. 2008. Antiepileptic drugs as human teratogens. *Expert Opin Drug Saf.* 7:195–209.
21. Mireku, M. O., M. J. Boivin, L. L. Davidson, S. Ouédraogo, G. K. Koura, M. J. Alao, et al. 2015. Impact of helminth infection during pregnancy on cognitive and motor functions of one-year-old children. *PLoS Negl. Trop Dis.* 9:e0003463.
22. Aderoba, A. K., O. I. Iribhogbe, B. N. Olagbuji, O. E. Olorok, C. K. Ojide, and A. B. Ande. 2015. Prevalence of helminth infestation during pregnancy and its association with maternal anemia and low birth weight. *Int. J. Gynaecol. Obstet.* 129:199–202.