

# Congenital Constriction Ring of Limbs in Subjects with History of Maternal Substance Use

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## ABSTRACT

Congenital Constriction Ring (CCR) is a rare malformation which manifests itself in the form of ring-like constrictive bands. Due to its heterogeneous nature, its etiology remains unclear. Here, we present a series of seven independent individuals afflicted with CCR, which primarily involved the digits. The phenotypic manifestations included terminal phalangeal reduction, anonychia, digit hypoplasia, and acrosyndactyly. Mesoaxial digits in hands and preaxial digits in feet were most frequently affected. Camptodactyly and clubfoot were witnessed in four and one subject, respectively. Curiously, mothers of six of these subjects revealed that they consumed copious amounts of *Multani mitti* (Fuller's clay) and/or *Naswar* (non-smoke-tobacco), during their respective pregnancies. Maternal substance use during pregnancy is not an unusual practice, however, its relationship with CCR as pregnancy outcome remains unexplored. Case-control studies are warranted to elucidate the relationship between the exposure to these substances and the etiology of CCR and/or other limb defects in the offspring.

**Key Words:** Congenital constriction ring. Amniotic bands. Digit anomalies. Acrosyndactyly. Substance use. Fuller's clay.

Congenital constriction ring (CCR; OMIM-217100) is a rare abnormality which manifests itself in the form of ring-like constrictive bands, usually in the limbs and occasionally in the trunk.<sup>1</sup> Isolated appearance is common while head and vital-organs are usually involved in the syndromic cases, leading to the suggestion of a term ADAM complex (amniotic deformity, adhesions, mutilations).<sup>1,2</sup> The etiology of CCR is not clear. It has been suggested that it may be caused by prenatal environmental factors, hemorrhages, and excessive movements of uterine muscles.<sup>2,3</sup> In this communication, we present seven independent cases exhibiting CCR, six of which had a positive history of maternal substance use.

Seven independent/sporadic cases, here described as subjects A-G, exhibiting CCR were ascertained during March 2010 and November 2013. The ascertainment of subjects was a part of an epidemiological study on limb defects carried out in different regions of Pakistan. The recruited subjects mainly belonged to rural, illiterate, nuclear-families and agro-business backgrounds (Table I). To observe the pregnancy histories, the available mothers of the recruited individuals were

retrospectively interviewed and data on familial/maternal risk factors were obtained. Constriction ring malformations with congenital presentations were included and traumatic cases were not considered. This study was approved by the Ethical Review Committee of the Quaid-i-Azam University, Islamabad.

CCR was confined to the digits/autopods in all subjects (Table I). Collectively, there were 17 affected limbs (10-upper, 7-lower), and 57 digits. In the upper-limbs, mesoaxial digits (2-3-4) were most commonly affected, while hallux was frequently involved in lower-limbs (Table I). There were four individuals with bilateral but asymmetrical limb involvement.

CCR phenotype was quite variable in the present cohort (Figures 1; A1-G4). The anomaly generally affected the digits at subcutaneous levels, but not affecting the bones, unless resulting in amputations (Table I). Amputations of certain digits were observed in 6 cases. However, there was only one example of mild post-constriction edema (subject 'C') (Figures 1; C1). Acrosyndactyly was evident in three subjects (A, B, F) (Figures 1; A1, B1, F1). Camptodactyly was accompanying CCR in four subjects (B, D, E, F). Dermatoglyphic changes, i.e., absence of triradii and the presence of simian crease, were evident (Figures 1; A1, F1). The cases were classified according to the Patterson (1961) scheme.<sup>3</sup> Most of the cases were of a severe nature, thus were concordant with type-3 and type-4. Clubfoot of the left foot was witnessed in subject 'G'.

The family histories were devoid of parental consanguinity (Table I). In-depth interviews with the subject's mothers revealed the frequent use of certain substances during the respective pregnancies. Four mothers disclosed that they used '*Multani mitti*' (Fuller's clay)

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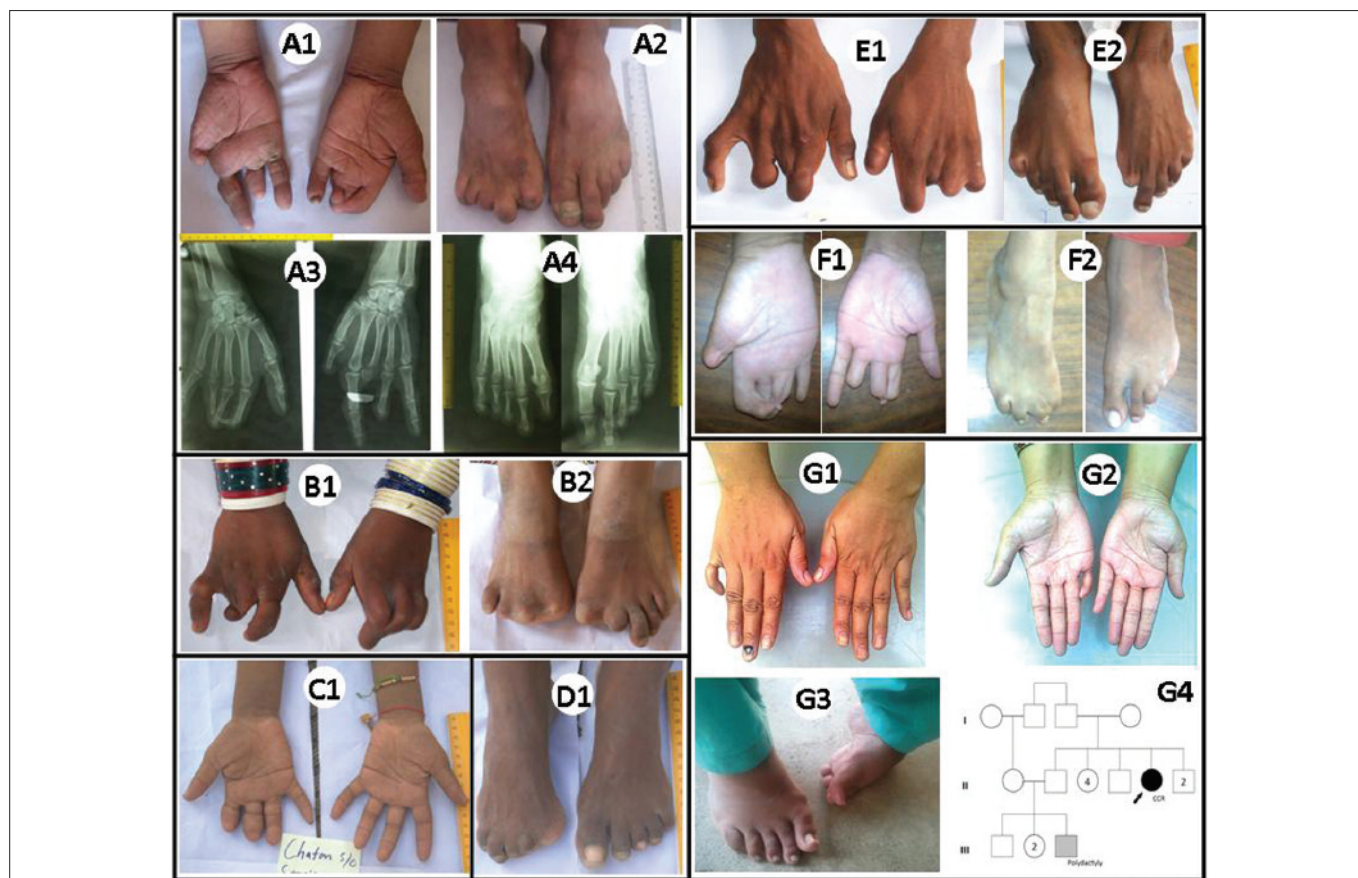
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**Table I:** Demographic features, familial attributes and phenotypic manifestation of subjects with CCR.

Variables	Subjects						
	A	B	C	D	E	F	G
<b>Demography</b>							
Gender / age	Male/40	Female/17	Male/10	Female/8	Male/20	Female/14	Female/30
Origin / religion	KPK/Islam	Sindh/Hindu	Sindh/Hindu	Sindh/Hindu	Sindh/Hindu	Sindh/Muslim	KPK/Muslim
Language / ethnicity	Hindko/Awan	Dhalki/Bheel	Dhalki/Bheel	Marwari/Bheel	Gujrati/Kohli	Sindhi/Muslim	Hindko/Awan
<b>Familial attributes</b>							
Paternal / maternal age at subject's birth (years)	40/25	43/34	20/17	32/27	40/35	27/23#	40/30#
Parity / gravida	5th-of-9	7th-of-8	2nd-of-4	4th-of-5	6th-of-7	3rd-of-4	7th-of-9
Maternal substance use	?	Multani mitti	Multani mitti	Multani mitti	Multani mitti	Multani mitti	Naswar
<b>Phenotype</b>							
Right hand	CR on digits 2,4; amputation at digits 1, 3 and 4	Amputation at digits 2-4; camptodactyly at digit 5	CR at digits 2-3; amputation of digit 4	—	Deficiency of digits 2-4; camptodactyly of digit 5	Deficiency in all digits acrosyndactyly at digits 2-4	5th digit, proximal phalangeal level
Left hand	Amputation at digit 5; acrosyndactyly of digits 2-3-4	Amputation at digits 2-5; acrosyndactyly of digits 2-3-4	—	Camptodactyly of digit 5	Deficiency of digits 1-5 at proximal phalangeal level	Deficiency in digits 2-4; acrosyndactyly at digits 2-3	—
Right foot	Terminal deficiency/anonychia at digits 1-4	Terminal deficiency of digits 1-4	—	Terminal deficiency of digits 1-3	—	Terminal deficiency at digits 1-3; fusion of digits 2-4	—
Left foot	—	Terminal deficiency of digits 1-2	—	Partial syndactyly of 2-4 toes	Deficiency of digit 1	Deficiency of digits 4-5; camptodactyly of digit 3	Clubfoot
<b>Classification</b> (Patterson, 1961)	1,3,4 (mixed)	3,4	3,4	4	3,4 (mixed)	3,4 (mixed)	1

# Parents were distantly related; CR = Constriction ring.



**Figure 1:** CCR phenotype. Subject-A (A1-A4); Subject-B (B1-B2); Subject-C (C1); Subject-D (D1); Subject-E (E1-E2); Subject-F (F1-F2); Subject-G (G1-G3). Pedigree of subject-G (G4).

during pregnancies while 2 mothers were using 'Naswar' (non-smoke-tobacco). Only subject 'G' had a second-degree relative which exhibited polydactyly (Figure 1; G4).

Four of seven present cases of CCR were ascertained through an epidemiological study aimed at establishing the spectrum of Congenital Limb Defects (CLDs) in Muslim and Hindu populations of interior Sindh.<sup>4</sup> There were a total of 165 cases of CLDs. Therefore, among the CLDs, CCR had an estimated proportion of 0.0242 (CI:0.0008 - 0.0477). Surprisingly, however, all of the CCR cases were clustered in the Hindu community and none of the case was witnessed in the Muslim cohort.<sup>4</sup> It is quite likely that specific risk factor(s) for CCR are exclusively associated with the Hindu community.

In rural areas of Pakistan, pregnant women do not undergo proper medical examination during pregnancies. They rely on domestic tips for obstetric problems and delivery. Consequently, there are very high rates of prenatal and maternal morbidities/mortalities.<sup>5</sup> Here, there were certain oral traditions about substance use. For instance, the pregnant mothers in Sindh had the belief that "Multani mitti made their fetuses strong, protected them from bad-souls, and made the delivery easier."

Previously, CCR and terminal transverse defects in the neonates have been proposed to be associated with maternal exposures to various drugs like misoprostol which is used in the treatment of duodenal/gastric ulcers and to terminate unwanted pregnancies.<sup>6</sup> For present cases, use of misoprostol in the periconceptional period can be ruled out mainly due to the unavailability of these drugs in remote rural areas. There is also increased risk of CCR in mothers exposed to vasoactive substances like cigarette smoking and aspirin. Maternal smoking is not common in Pakistan and information on use of

Naswar is scarce. The authors, however, did not collect data on the use of aspirin.

Acrosyndactyly was accompanying CCR in three of seven cases presented here. Severe type of clubfoot was observed in one subject which is a rare observation. Furthermore, none of these cases were primigravida, which is contrasting to the previous observations.<sup>6,2</sup>

This study, however, does not present the quantitative analyses of amount of substance use, the specific period during pregnancy and the length of exposure. It would be worthwhile to launch a case-control study in order to ascertain the relationship between CCR in newborns and the maternal exposure to these substances.

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