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Clinical evidence of the association between radial longitudinal deficiency and radial polydactyly: a case series

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Abstract

Radial longitudinal deficiency (RLD) is commonly associated with thumb hypoplasia. The association between RLD and radial polydactyly (RP) is uncommon, but case reports or case series have been reported. We report our experience of managing patients with this association. A total of 97 patients with RLD were seen in our department, of which six were children with concomitant RLD and RP. Four children had both RLD and RP in the same limb; of them, three also had RLD in the contralateral limb. The mean age at presentation was 11.6 months. Awareness of this association alerts the clinician to look for RLD in the presence of RP and vice versa. This case series supports recent experimental and clinical evidence that RP and RLD may be part of the same developmental spectrum. Further studies may guide its inclusion as a possible new category in the Oberg-Manske-Tonkin (OMT) classification of congenital upper-limb anomalies.

Level of evidence: IV

Keywords

Radial dysplasia, longitudinal deficiency, preaxial polydactyly, thumb duplication, sonic hedgehog

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Introduction

Radial dysplasia is usually associated with hypoplastic thumb as part of a radial longitudinal deficiency spectrum (RLD). In the embryo, the anteroposterior (radio-ulnar) axis is controlled by the 'Zone of Polarizing Activity' (ZPA), which consists of mesenchymal cells on the posterior margin of the limb bud. These cells express the sonic hedgehog (SHH) protein, first reported by Riddle et al. (1993), which is set up as a SHH concentration gradient across the anteroposterior axis with maximum concentration on the ulnar (posterior, little finger) side and minimal concentration on the radial (anterior, thumb) side. SHH induces the formation of the ulna and the ulnar four digits while the radius and thumb develop largely in the absence of SHH signalling (Harfe, 2011, Oberg et al., 2010). There has been recent experimental evidence that ectopic expression of SHH in the anterior margin of the developing limb bud supresses radial development and induces the formation of a variety of anomalies, including radial hypoplasia, thumb hypoplasia and deficiency of other radial structures (Lam et al., 2019). However, radial polydactyly (RP) also appears to be induced by ectopic SHH expression in the anterior limb bud, giving rise to the theory that RP and RLD could be part of the same embryonic spectrum, a theory first proposed by Al-Qattan (2012) and further supported by a case series of families with this association (Al-Qattan, 2018a).

We report a further six cases of patients with concomitant RLD and RP who presented to our institution, and studied their demographics, clinical features and other associated conditions. This information will

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hopefully lend more support to the experimental and clinical evidence that these two conditions may be caused by the same aberrant SHH signalling milieu, and guide clinicians when faced with these two seemingly different entities.

Methods

We searched our database for patients with RLD (entire upper limb) seen at Ganga Hospital, Coimbatore, India between June 2001 and February 2023 and included only those medical records that had documented photographs or radiographs. Our institution does not require ethical approval for reporting individual cases or case series.

A total of 97 patients who visited us during this period with RLD affecting the entire limb were studied to find the occurrence of RP. Six children with RLD and RP in the same or contralateral limb were included in the study. Their antenatal and family history, clinical findings and surgical details were recorded in detail. The main variables studied were consanguinity of marriage, birth order, age at first presentation to our unit, gender distribution, clinical phenotype, associated anomalies and syndromic associations. The classification of RLD was carried out using the modified Bayne and Klug classification (Bayne and Klug, 1987; Goldfarb et al., 2005; James et al., 1999).

Results

The mean age of these six children at the time of presentation was 11.6 months (range 18 days to 3 years). Both sexes were affected equally. RLD and RP were seen together in the same limb in four children and in different limbs in the remaining two children. Three of these four children had RLD with thumb hypoplasia or triphalangeal thumb in the contralateral limb. The clinical details of each of the six children are described (Figures 1–6).

Four children had associated congenital heart disease, which included valvular pulmonary stenosis, ventricular disparity of the heart with a persistent superior vena cava, and two had atrial septal defects. Only one child had features fitting the diagnosis of a syndrome: vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomaly and limb anomalies (VACTERL). This child had a high anorectal malformation, congenital heart disease in the form of ventricular disparity of the heart and a persistent superior vena cava, microcephaly, cleft palate and mild scoliosis.

Parents of two of the patients had a consanguineous marriage, where the father married his uncle or aunt's granddaughter. All of the patients were their parents' first-born child except one who was the second-born child. RLD was reported in subsequent pregnancies of a mother who opted for termination. A history of infertility was noted in one case where the child was conceived through intra-uterine insemination (IUI) after two failed IUI attempts. The antenatal history of the mothers was uneventful except for the presence of gestational diabetes in one, antepartum haemorrhage in one, COVID-19 infection in one and polyhydramnios in two mothers. Four children were delivered by caesarean delivery. A positive family history of similar hand conditions was present in a patient's father's cousins who also presented with foot deformities, the description of which matched that of club foot.

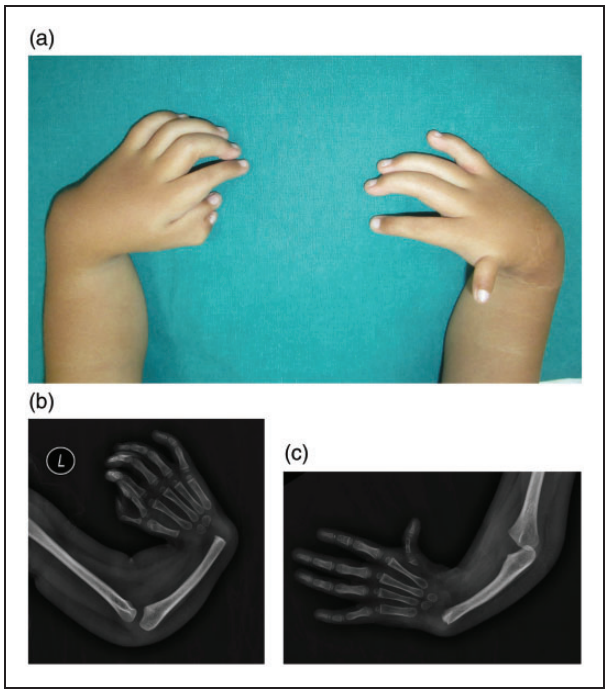

Figure 1. Clinical pictures of a 3-year-old girl. (a) Bilateral radial aplasia (Modified Bayne and Klug type IV) with floating right thumb (Modified Blauth type IV hypoplasia) and left radial polydactyly (Wassel type IV). Radiographs of (b) left upper limb and (c) right upper limb.

Discussion

Although uncommon, our case series of six children provides further clinical evidence to support the clinical association of RLD and RP as reported previously (Al-Qattan 2018a; Al-Qattan 2018b; Marangoz and Leblebicioğlu, 2006; Rotman and Manske, 1994; Yildirim et al., 2005).

The first report of this uncommon association was by Rotman and Manske (1994), where they described

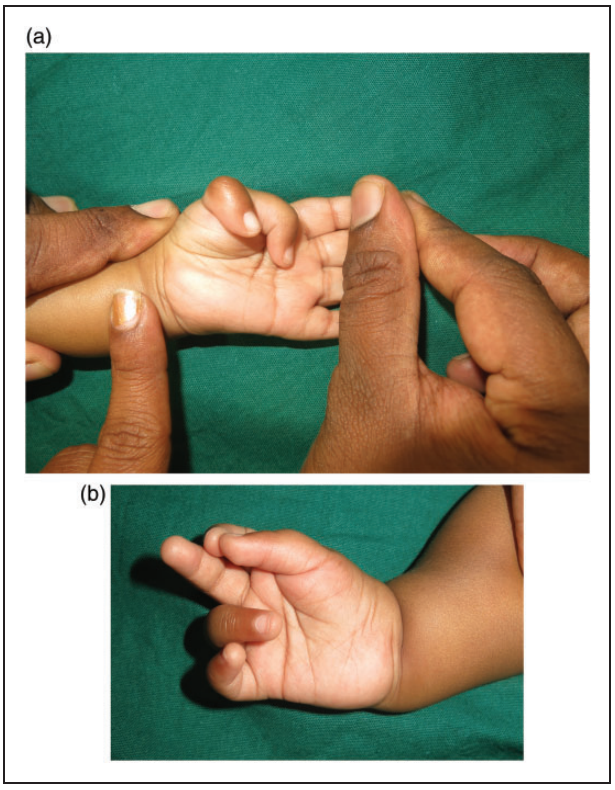

Figure 2. Clinical pictures of a 6-month-old boy. (a) Left radial polydactyly (Wassel type IV) with radial hypoplasia and (b) Right radial hypoplasia (Modified Bayne and Klug type II) with a hypoplastic thumb.

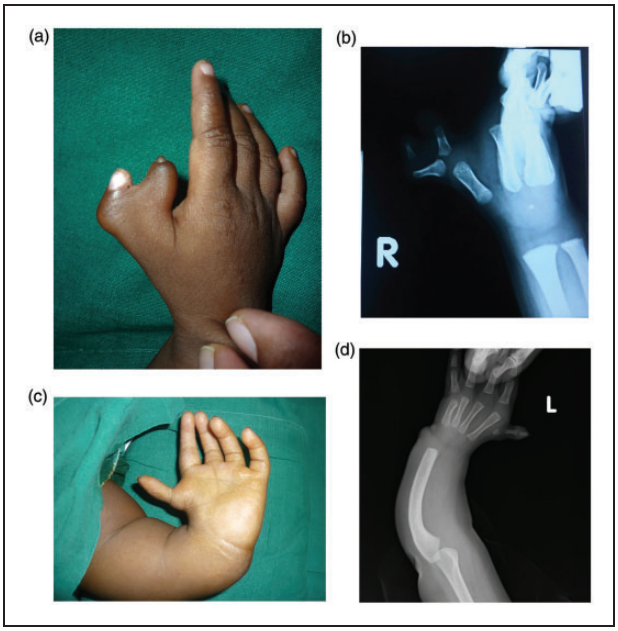

Figure 3. Clinical pictures and radiographs of a two-year-old boy. (a, b) Wassel type IV radial polydactyly on the right and (c, d) Type IV radial dysplasia and a Modified Blauth type 3C hypoplastic thumb on the left.

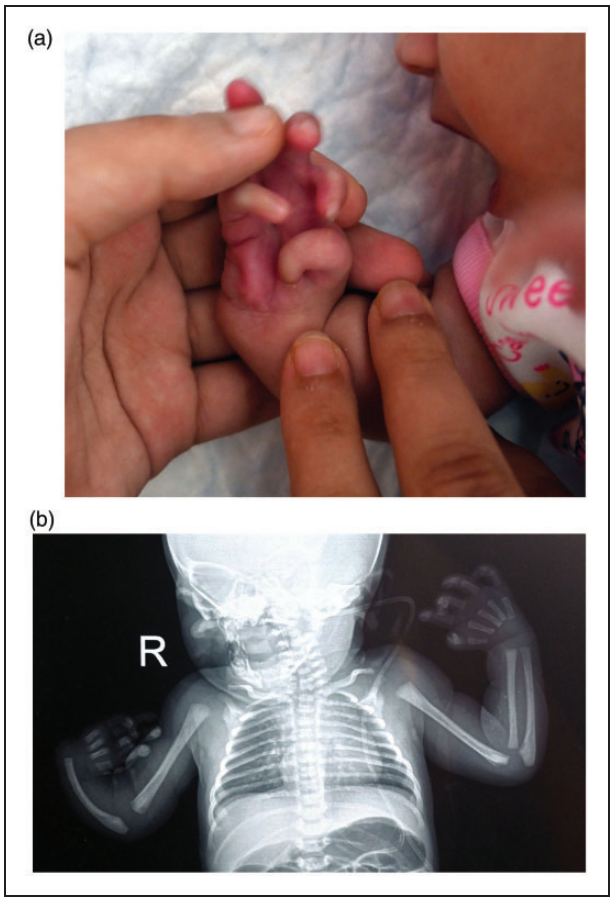

Figure 4. Clinical pictures of a 25-day-old girl. (a) Right thumb-in-palm deformity with a radially deviated wrist and (b) Radiograph showing right triphalangeal thumb with absent radius and left duplicated distal phalanx of the thumb with a shortened radius.

an infant with RLD and contralateral RP. This was followed by reports of thumb triplication with RLD (Marangoz and Leblebicioğlu, 2006; Yildirim et al., 2005). More recently, Bauer et al. (2020) described a similar association, except their focus was on thumb hypoplasia, which was considered part of the RLD spectrum. Of the 132 patients who presented with RP, 11 had concomitant thumb hypoplasia, once again highlighting the importance of looking out for an unexpected hypoplasia/polydactylous association as part of the same disease spectrum in the same patient.

Alterations in SHH expression have been shown to be responsible for various limb-patterning defects (Bastida et al., 2009; Bouldin et al., 2010; Riddle at al., 1993; Tickle et al., 1975; Tickle and Towers, 2017; Tiecke and Tickle, 2007; Towers et al., 2012). Marangoz and Leblebicioğlu (2006) earlier attempted to explain the phenomenon of a combined morphology of RP and RLD through either a continuous insult

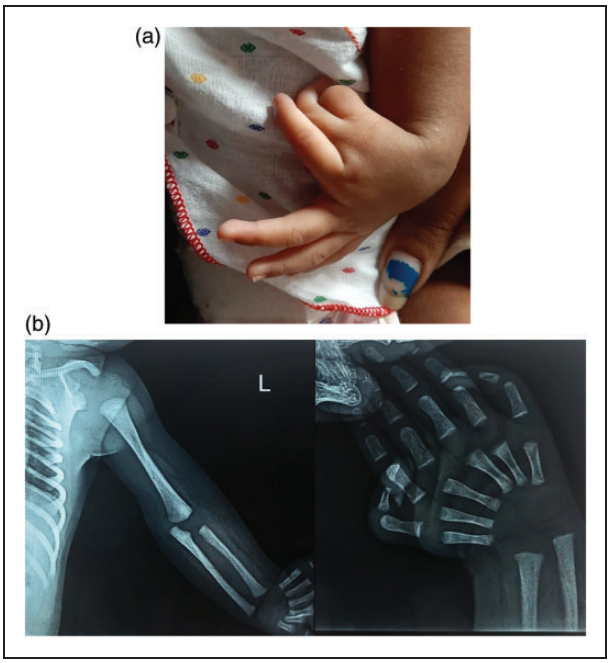

Figure 5. A six-fingered left hand in an 18-day-old girl. (a) Radial polydactyly and partial syndactyly of the radial two digits with flexion and radial deviation of wrist. Elbow flexion was limited and (b) Radiographs showing radial hypoplasia and a six-digit hand.

or multiple insults during hand development. However, the possibility of RLD and RP being the result of the same embryonic event as influenced by aberrations in the SHH pathway was first proposed by Al-Qattan (2013). He suggested a spectrum whereby a minor increase in SHH causes duplication of the thumb, a moderate increase leads to the formation of a triphalangeal thumb or triphalangeal component or triplicated thumb, and that RP with RLD and the non-classic forms of mirror hand anomaly are caused by a significant increase in ectopic expression of SHH.

In 2018, Al-Qattan further described a case series of nine families where there was an association between RP and RLD. Contrary to our paper, which concentrated on forearm anomalies, Al-Qattan (2018a) included cases of thumb hypoplasia without radial hypoplasia and great toe duplication without thumb duplication in his report on nine families. Among the 14 patients in the nine families, two entities were not co-existent in members of two of the families and 3 of 14 patients had concomitant RLD and RP, among whom only one had both in the same limb. We had only one child with syndromic association, and the phenotypes seen in our series seem to differ from the previous reports.

The clinical observation of this uncommon association sheds more light on the pathogenesis of some of the commonest conditions seen in congenital hand differences, including RP, thumb hypoplasia and radial aplasia. The association between these conditions would seem contradictory, with RLD and thumb hypoplasia usually classed as 'deficiency' conditions or a 'failure of formation', whereas RP would be seen as more of a proliferative condition or 'duplication'.

The action of ectopic SHH probably occurred via a mutation in the limb-specific enhancer region of the upper limb, known as the ZPA Regulatory Sequence (ZRS) (Lettice et al., 2003). ZRS enhancer mutations combine with secondary long-range SHH signalling effects to cause RP in Silkie chicken experiments (Johnson et al., 2014). Initial expression is driven by this mutation, but results in an ectopic, automated positive loop, including SHH and fibroblast growth factor (FGF). When this feedback loop increases in intensity, or when it occurs earlier or later, various phenotypes result. Similar to the hypothesis proposed by Al-Qattan (2012), experimental evidence demonstrated that early ectopic SHH expression can lead to thumb/radial hypoplasia while a late expression can cause thumb polydactyly, as radius specification/patterning occurs before digital patterning (Lam et al., 2019; Tickle and Towers, 2017). The mirror hand or ulnar dimelia condition is probably the result of an earlier, more sustained expression of ectopic SHH on the anterior limb bud (Figure 7).

Interestingly, our cases series illustrates the different combinations of the two entities that were suggested in the chicken limb experiments. The RLD-RP co-existence in the same limb (Figures 1, 2, 4 and 5) might be due to 'early strong and prolonged ectopic SHH expression' in the limb bud. Bilateral involvement (5/6 children) with phenotypical differences between the limbs might be due to different effects of gene mutations on the SHH signalling in the two limb buds. Even in a normal embryo, initial SHH protein concentration varies from limb to limb due to the difference in the number of SHH-producing ZPA cells or initial amounts of SHH protein (Harfe, 2011).

Case 5 (Figure 5) in our series, with ipsilateral RLD and RP in a six-fingered hand, can probably be placed somewhere between RLD and mirror hand in the spectrum of embryonic effects of ectopic SHH expression (Lam et al., 2019). In this case, the aberrations in SHH signalling were probably not enough to progress to duplication of the ulna and the ulnar digits (ulnar dimelia). The possibility of a Type 3B intermediate type of mirror hand deformity (with multiple fingers with an ulna and a hypoplastic radius) cannot be ruled out as it resembles the eight-fingered hand reported by Al-Qattan et al. (1998).

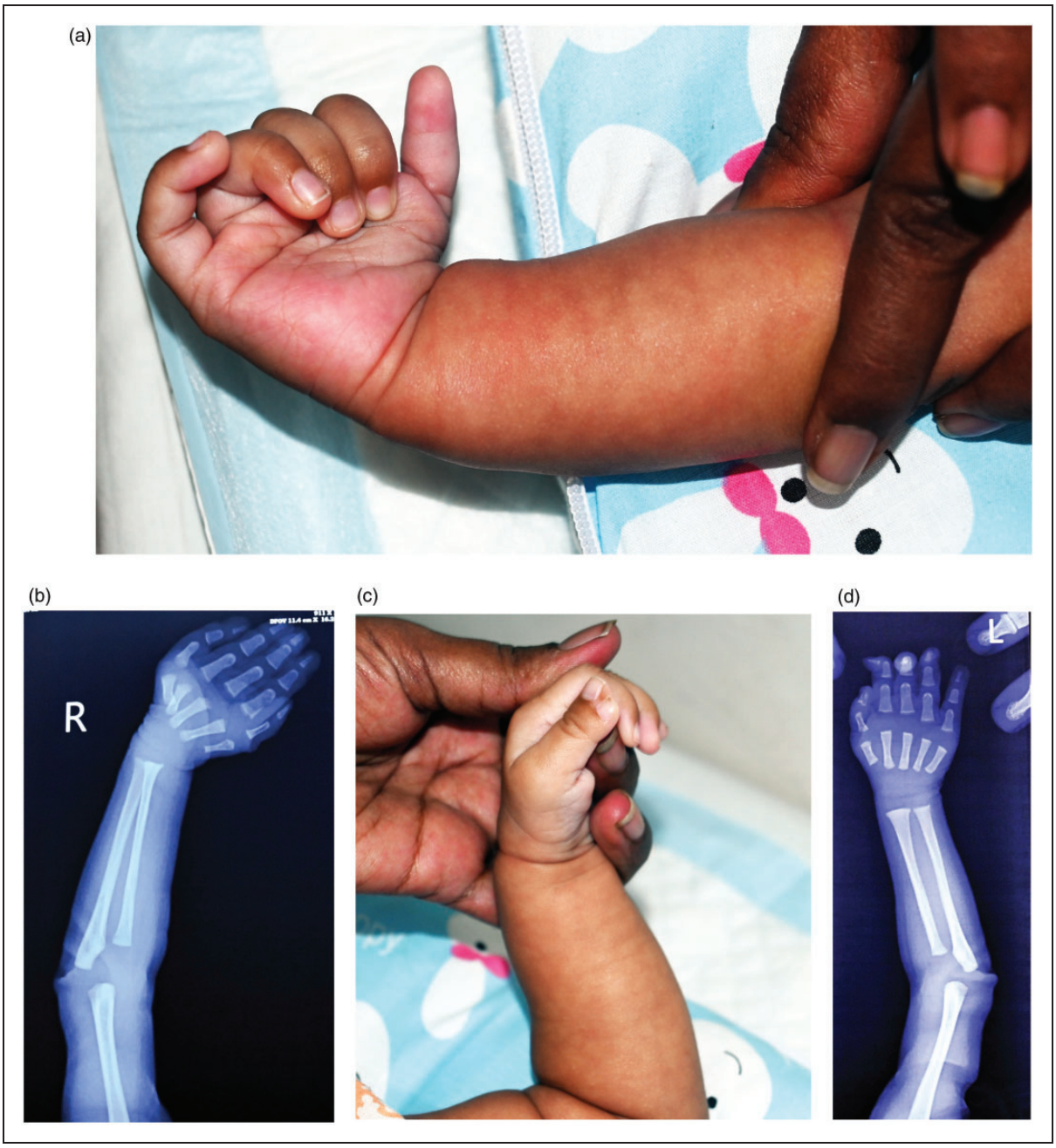

Figure 6. Clinical pictures and radiographs of a 2-month-old boy. (a, b) A radially deviated wrist with a hypoplastic thumb (Modified Bayne and Klug type 0) on the right and (c, d) Duplicated thumb (Wassel type II) on the left.

At present, the Oberg-Manske-Tonkin (OMT) classification of congenital upper-limb anomalies adopted by the International Federation of Society for Surgery of the Hand (IFSSH) (Goldfarb et al., 2020) places RP and RLD in separate classifications as part of the anteroposterior malformation axes (entire upper limb and hand plate). Thumb hypoplasia is considered to be part of the RLD spectrum, classified as 'radial longitudinal deficiency, hypoplastic thumb'. There is presently no consideration for RP to be considered in the same group as radial aplasia/hypoplasia, i.e. 'radial longitudinal deficiency, radial polydactyly', and perhaps this should remain the case as the association is so uncommon. However, clinicians should be open to the possibility of these two conditions occurring in the same patient, as they share the same embryonic spectrum, which is the purpose of this report.

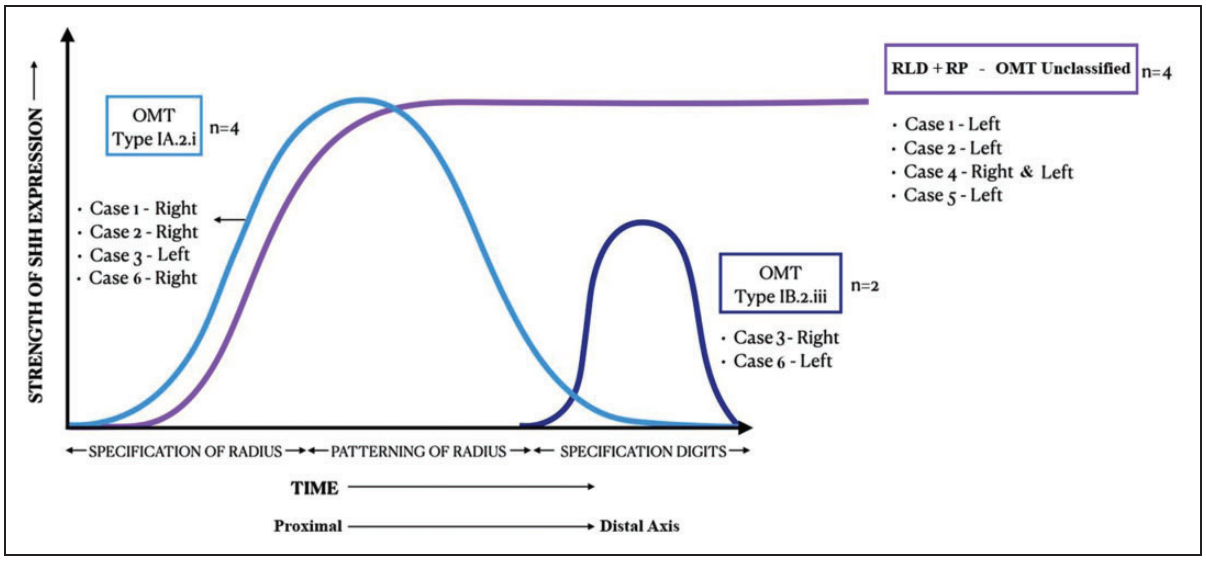

Figure 7. Graph correlating the SHH signalling strength with time of limb development. When low-strength ectopic SHH expression can result in preaxial polydactyly, moderate concentration is required for radial dysplasia to occur, and even higher amounts are required to form a mirror hand with two ulnae. Specification and patterning of the radius take place before digital patterning. The nine affected limbs have been classified according to the updated OMT classification and are placed in the limb development timeline.
OMT: Oberg-Manske-Tonkin; Type I – Malformations, A – Entire upper limb, B – Hand plate, 2 – Radial-ulnar (anterior-posterior) axis, IA.2.i – Radial longitudinal deficiency and IB.2.iii – Radial Polydactyly; SHH: sonic hedgehog.

Another clinical implication of this study is to encourage clinicians to look for hypoplasia of any radial structures when encountering a patient with RP (Bauer et al., 2020) as this may allow surgical correction to be completed in a single stage.

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