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Review Article

Intrauterine Random Premature Physeal Arrest: Case Report and Literature Review

William J Shaughnessy* and Hamlet A Peterson

Department of Orthopedic Surgery, Mayo Clinic, Rochester, USA

***Address for Correspondence:** William J Shaughnessy MD, Department of Orthopedic Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA, Tel: 507-284-2883; Fax: 507-284-8935; E-mail: shaughnessy.william@mayo.edu

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ABSTRACT

Fetal intrauterine premature random partial or complete physeal arrest is a rare, previously unreported congenital deformity. This paper presents a neonate with a fetal intrauterine vascular insufficiency of one upper extremity present at birth, which subsequently developed multiple random premature physeal arrests, all distal to the site of the vascular insufficiency. Some of the physeal arrests were complete, some partial, and some physes remain normal. The distal humerus, proximal and distal radius and ulna, and two metacarpals all have premature physeal arrests. The first metacarpal physeal bar and second metacarpal physeal bar equivalent were excised at age 7 years I month. The result of the surgery and the ultimate limb deformity may not be known for several years.

Although neither the exact dates, nor the age of the fetus at the time of the intrauterine injuries are known, the radiologic identification of metaphyseal-physeal abnormalities at multiple sites at age 32 days of life, represents the youngest recorded patient to have comparison x-rays which document multiple random ischemic physeal arrests. This is also the first recorded patient with intrauterine vascular deficiency to have surgical excision of either a physeal bar or a physeal bar equivalent.

The purpose of this article is to encourage orthopedic surgeons to be involved in the initial and extended care of patients with neonatal limb vascular deficiency with one of the goals being early identification of bone growth abnormality.

Keywords: Intrauterine vascular insufficiency; Gangrene; Physis; Physeal bar; physeal bar equivalent

Case Report

This baby girl was born at 38 weeks 4 days gestation via vaginal vertex delivery after 12 hours labor of the mother's first and uncomplicated pregnancy. Ultrasound examinations at 8 and 20 weeks were both normal. Birth weight was 3320 gms, (7 lbs. 5 oz.), Length 31 cm, (19.5 inches). Blood type O^+, same as the mother. The parents have since produced a normal second child.

Examination of the infant at birth was normal except for a "smaller, shorter left forearm" with a "left wrist drop". There were irregular patches of ecchymosis and skin necrosis about the left elbow and forearm (Figure 1). The left upper extremity was essentially flail. There was active motion of the shoulder and "maybe some active biceps, but little if any forearm, wrist or hand motion". The recorded diagnosis was "possible compression injury with open wound in pregnancy".

On day 6, the lesions manifest as three areas of dry gangrene on the proximal lateral aspect of the left forearm, a "white eschar" on the proximal anterior aspect of the left forearm (Figure 2), and soft tissue atrophy beneath and distal to the lesions. The lesions displayed no sign of infection and were treated non-operatively with local wound care. The gangrenous areas spontaneously sloughed and were healed secondarily with normal skin. No surgical debridement or skin grafting was performed.

The patient's first extremity x-rays, taken at 32 days of life, showed

mild flattening, subchondral lucency and sclerosis of the metaphyses of the left distal humerus, proximal and distal radius, and a notch in the distal ulnar metaphysis as compared to the right (Figure 3A and B), indicative of adjacent physeal abnormality. As expected there was no ossification in the corresponding epiphyses at his age.

At age 7 years 1 month of age the patient had an arm length difference. The forearm length from the elbow flexion crease to the wrist flexion crease was 17.5 cm on the right and 12.5 cm on the left (Figure 4). She was right hand dominant, but was able to grab objects in opposition on the left. Hand sensation was intact. Finger flexion, PIP and DIP extension were normal. Active wrist and MP joint extension was absent. The wrist had a mild ulnar plus deformity with little passive volar flexion beyond neutral. Forearm active and passive pronation was to neutral, while active supination was 20º and passive supination 45º. There was a 30º left elbow flexion contracture with active and passive flexion to 140º. The skin was mobile and did not contribute to her elbow flexion contracture. There was diminished or nonexistent extensor muscle mass on the lateral proximal forearm. The thumb and index finger were shorter than those on the right. The child had normal stature documented on more than 15 occasions during her first 7 years of life. She had no clinical or radiographic evidence of a skeletal dysplasia, Madelung deformity or other skeletal anomalies.

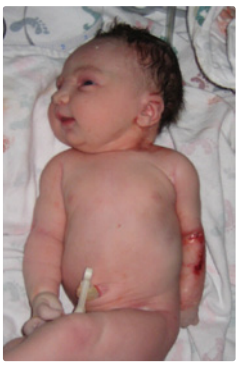


Figure 1: At birth the left forearm was smaller than the right and there were irregular patches of ecchymosis and full thickness skin necrosis on the lateral left forearm.

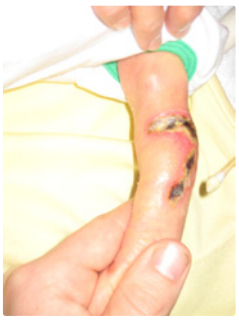
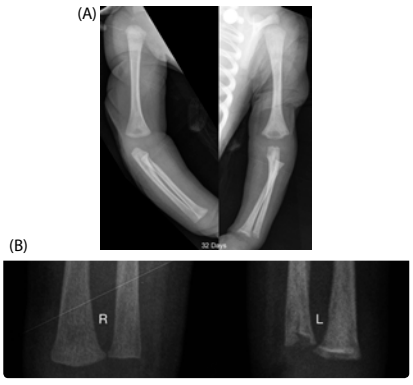
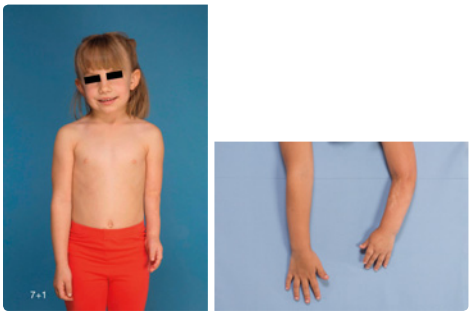


Figure 2: At six days of life there are three well-developed gangrenous black eschars on the left upper forearm and a "white eschar" distal to the anterior elbow crease.



Figures 3a,b: Roentgenograms of both arms at 32 days of life. a: The left distal humeral metaphysis is more sclerotic and irregular, and the length of the metaphysis between the distal olecranon fossa and the physis is less, than on the right. There is sclerotic flattening of the proximal left radius and ulna. b: The left distal ulnar metaphysis is abnormally notched and radiolucent. Each of these abnormalities portend adjacent physeal vascular insufficiency or malfunction. As expected there is no epiphyseal or carpal ossification.



Figures 4a,b: At age 7 years 1 month the left upper arm, forearm, thumb, and index finger, are shorter than the right.

Roentgenographs of the left hand and wrist show deformed and sclerotic distal radial and ulnar metaphyseal-physeal junctions with impaired ossification of their epiphyses, indicative of lack of growth of their physes (Figure 5). The left radius measured 10.4 cm in length compared to 15.9 cm on the right. The left ulna measured 12.7 cm compared to 16.8 cm on the right. The distal ulna was slightly longer than the distal radius producing a mild clinical wrist ulnar plus deformity, suggesting some growth of the proximal ulna. The thumb and index fingers were short relative to the ulnar three fingers due to a central physeal bar in the thumb metacarpal, and a physeal bar equivalent [1] (no bridge of bone from metaphysis to epiphysis) in the index finger metacarpal (Figure 6). The ulnar three metacarpal and all phalangeal physes are normal. The pattern of physeal abnormalities was consistent with the original soft tissue lesion on the radial forearm, suggesting more involvement of radial artery perfused structures. The ulnar side of the forearm and hand were relatively spared in comparison.

At age 7 years 1 month the thumb metacarpal physeal bar and the index finger metacarpal physeal bar equivalent were surgically excised. Cranioplast was used as the interposition material. Several years of observation may be needed to determine the result.

Review of the Literature

Numerous cases of vascular insufficiency of an extremity occurring in utero antenatally have been recorded in the literature [2-55] (Table 1). Only four of these articles appear in journals commonly

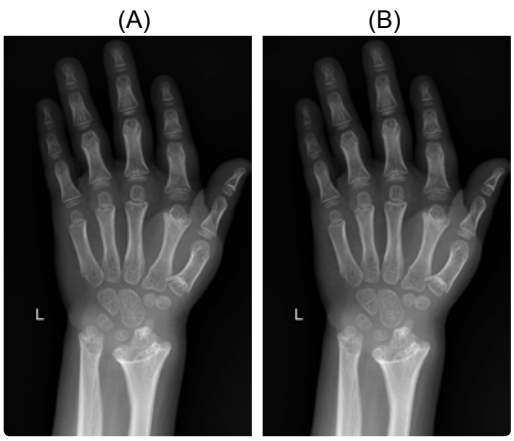


Figure 5a,b: Roentgenograms of the left and right hand at 7 years 1 month. The distal radial and ulnar metaphyses are sclerotic, flat, and irregular. There is little or no ossification in their epiphyses. The thumb and index finger metacarpals are relatively short. The metaphyses, epiphyses, and physes of the lateral three metacarpals, and all finger phalanges, are normal. The right hand and wrist are normal.

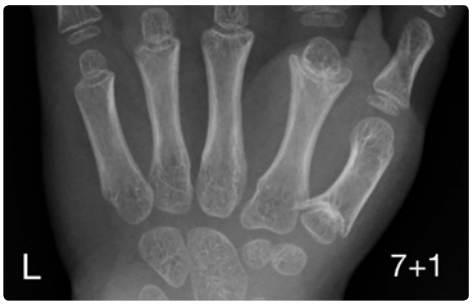


Figure 6: The thumb metacarpal proximal physis is cupped and has a central physeal bar. The index finger metacarpal distal physis is cupped, but has no physeal bar (a physeal bar equivalent [1]).

reviewed by orthopedic surgeons [17,37,45,47]. The incidence may be decreasing due to improvement in perinatal care [36]. Not included in this review are an even larger number of references in which similar findings first occurred hours or days after birth, and cases published in languages other than English. The twin-to-twin transfusion syndrome with monochorionic twin pregnancy also results in frequent limb vascular insufficiency anomalies. Since the patient presented here was not a twin, this literature is also not included. The most frequent expression of vascular insufficiency in the titles of the included articles is the term "gangrene".

Most previous reports describe single cases (Table 1). Two articles describe multiple cases [54,55] but do not provide individual case data as documented in Table 1. One report [4], which presented one case, reviewed 39 patients in 39 previous articles published between 1828 and 1939 mostly in foreign languages, made no mention of x-rays in any case.

Cases predominate in the upper extremities 53/10 (84%), in males 34/17 (67%), and on the right side 34/21 with 4 bilateral (R-58%, L-36%, & Bilat. 7%) (Table 1). The reasons for these differences are unknown, but the figures are similar to a previous review [33].

Radiographs have been underutilized (Table 1). Four patients had x-rays of the involved extremity taken on the day of birth [26,31,35,36]. None had comparison x-rays. All images were reported to be normal, but the printed radiographs are small and of such quality that no statement can be offered concerning their physes. One x-ray taken at 1 month of age showed an anterior dislocation of the proximal radius with an indistinct metaphyseal-physeal border [39]. Four articles showed absent or delayed epiphyseal ossification centers, and lack of growth in various stages from 8 months to 5 years [31,33,36,38]. One article showed a single patient with marked radial and ulnar relative shortening at 13 years [31]. Only three articles mention the lack of bone growth [38,39,55], and only three articles mention the physis [42,50,55].

Of the 62 cases reviewed in Table 1, one was stillborn [13], one had auto-amputation at 5 weeks [14], 18 had surgical amputation within 3 months [5,8,11,18,20,21,25,27,36,40,42,43,45,47,49,52], and 6 died within 4 months [3,5,7,15,16,29]. The majority retained the involved extremity, but usually had limb scarring, contracture, deformity, atrophy and/or relative shortening. In one case with relative forearm shortening, the hands were noted clinically to be the same size with normal function at age 6 years [38], suggesting normal hand physeal growth. One infant with a skin graft was "healing" at 2 months [53], three patients were "normal" at 6 weeks [12], 7 weeks [9], and 6 months [19], one patient had "full function" at 22 months [41], and one patient was lost to follow-up at 6 weeks [24].

Findings

The findings of fetal intrauterine vascular deficiency at birth are variable, and include cold ischemic skin, pallor or reddish, blue, or purple discoloration (cyanosis), mottled with blister-like lesions (bullae), diminished or absent pulses with delayed or no capillary refill (vasospasm), and low or no blood pressure. The extremity may be swollen (edema) with underlying decreased muscle tone (flaccidity) or limitation of motion (paralysis). Variable areas of dry eschars (gangrene) may be present at birth or develop in the following hours or days. The gangrene is typically dry; infection is rare. The vascular impairment is rarely limited to the skin and subcutaneous tissues; it may also involve underlying muscles, nerves, and bones to various degrees. The time and duration of the ischemic event (or events) are also usually unknown.

After such an ischemic event, tissue impairment may range from mild and reversible to severe and irreversible. The extent of permanent damage depends on the degree of vascular insufficiency and the ability of collateral circulation to compensate for the diminished circulation. When gangrene is established at birth, auto amputation, surgical amputation, or some permanent loss of function is common.

The most important differential diagnosis with this condition is Necrotizing Fasciitis of the Newborn, which is characterized by a moist wound, fulmination infection, rapidly developing sepsis, and progressive tissue destruction [17,24,25]. Other possibilities include congenital limb deficiency or skeletal dysplasia, but it is rare to have gangrene present at birth in these conditions.

Etiology

Many hypotheses of intrauterine fetal limb vascular deficiency present at birth have been proposed, but are rarely substantiated in an individual case. These causes can be classified into extrinsic and

Table 1: Vascular insufficiency of an extremity present at birth (Since the advent of x-ray).

Year	Author*	Gender	Extremity	Photo at birth	Age bone x-ray published	Age at last follow-up	Outcome
1901	Bronson EB [2]	F	R Shoulder & Hand	+	---	11 weeks	Lesions sloughing
1904	Cotes-Preedy D and Cantab MA [3]	---	R Leg and Foot	---	---	1 day	Died on day 1
1941	Heller G and Alvari G [4]	M	R Forearm	+	---	48 days	Forearm atrophy
1945	Steiner MD [5]	M	L Forearm & Hand	---	---	3 months	Amputation d. 11, Died 3 m.
1950	Perlmutter HD and Wagner DH [6]	M	R Lower Extremity	---	---	16 months	"Physically retarded"
1951	Brown RJK and Smith SRN [7]	M	L Forearm	+	---	3 days	Amputation day 1, Died d 3
1952	Askue WE and Wong R [8]						
		F	L Forearm & Hand	+	---	34 days	Amputation on day 28
1953	Stadler HE [9]	---	Bilateral Feet	+	---	7 weeks	Normal
1959	Brock BH [10]	M	R Leg	---	---	6 weeks	Deformed, scarred leg
1960	Copeck G and Tassy F [11]	M	R Forearm & Hand	+	---	2 months	Amputation on day 4
1965	Braly BD [12]	M	R Lower Extremity	---	---	6 weeks	Normal
1970	Gilbert EF, et al. [13]	M	R Lower Extremity	+	---	Stillborn	Stillborn
1971	Glaun BP, et al. [14]	M	L Foot	+	---	5 weeks	Auto amputation of toes
1971	Siegel LK and Gross R [15]	---	L Arm	---	---	24 hours	Died
1974	Hoffman S, et al. [16]	F	R Forearm & Hand	+	---	12 days	Died
1975	Hensinger RN [17]	---	L Upper Extremity	+	---	14 months	Contracture, scarring
1976	Jaiyesimi F, et al. [18]	M	R Forearm & Hand	+	---	9 weeks	Amputation on day 24
1977	Fee HJ, et al. [19]	M	R Forearm & Hand	---	---	6 months	Normal
1977	Ward TF [20]	M	R Forearm	+	---	7 months	Amputation at 2 months
1977	Wiseman NE, et al. [21]	M	L Forearm & Hand	+	---	6 months	Amputation at 1 week
1979	Tsur H, et al. [22]	---	L Forearm	+	---	3 years	Wrist flexion contracture
1983	Christianson SD, et al. [23]	F	Bilat Hands and Feet	+	---	10 days	"Tissue loss"
1984	Rayner CR, et al. [24]	M	L Forearm & Hand	+	---	6 weeks	Lost to follow-up
1984	Shaffer WO, et al. [25]	M	R Forearm & Hand	+	---	11 days	Amputation on day 11
1985	Hsi AC, et al. [26]	F	R Forearm	---	At birth	6 months	Atrophy, no motor function
1988	Johnson D, et al. [27]	---	Bilat Upper Extrem.	+	---	1 week	Amputation, bilat on day 3
1989	Katzman GH [28]	M	R Forearm &Fingers	+	---	53 days	"Tissue sloughing"
1989	Van Allen MI, et al. [29]	F	R Forearm & Hand	+	---	22 days	Died
1991	Duncan BW, et al. [30]	M	R Forearm &Fingers	+	---	12 days	Lesions healed primarily
1992	Caouette-Laberge L, et al. [31]	M F M F M	L Forearm & Hand R Forearm & Wrist R Forearm R Forearm - Distal Forearm	--- + --- + ---	13 years At birth, 2 & 5 years --- --- ---	13 years 2 & 5 years 5 years 2 years 2 years	Marked forearm shortening Hand ulnar deviation Hand soft tissue surgery Forearm 1.5 cm shorter Forearm 1.5 cm shorter
1992	Kline SC and Moore JR [32]	M M	L Forearm & Hand L Forearm	+ +	--- ---	3 months 18 months	Good motor function Good motor function
1992	Turnpenny PD, et al. [33]	F	L Forearm	+	At 8 mths	9 months	Shortened forearm
1994	Guajardo L, et al. [34]	F M	L Upper Extremity Both Upper Extrem.	--- ---	--- ---	12 days 7 days	Swelling left arm Decreased muscle tone
1995	Ricciardelli E, et al. [35]	F	R Upper Extremity	+	At birth	2 years	Atrophy, impairment
1996	Carr MM, et al. [36]	M	R Forearm & Hand	+	At birth & 18 month	3 years	Amputation of fingers
1996	Farrar MJ, et al. [37]	--- ---	Forearm & Fingers Forearm & Fingers	--- ---	--- ---	--- ---	Shortened forearm Shortened forearm
1997	Tsujino A, et al. [38]	F	R Forearm	+	At 2 & 4 years	6 years	Shortened forearm
1999	Nagore E, et al. [39]	F	R Forearm	+	At 1 month	4 months	Hypertrophic scar

1999	Tebes CC, et al. [40]	M	R Forearm & Hand	+	---	15 months	Amputation at 9 days
2000	Gosain AK, et al. [41]	F	L Forearm & Hand	+	---	22 months	Full function
2000	Özgenel GY, et al. [42]	M M	R Forearm L Hand	--- +	--- ---	"Days" "Days"	Amputation Amputation
2002	Long DK, et al. [43]	F	L Leg & Foot	+	---	4 weeks	Amputation at 3 hours
2004	Cham PMH, et al. [44]	F	L Forearm	+	---	23 months	Forearm hypoplasia
2006	Jones DB, et al. [45]	M M	R Upper Extremity R Upper Extremity	+ +	--- ---	3 weeks 11 months	Forearm "tightness" Amputation of fingers
2007	Bednarek N, et al. [46]	--- ---	R Forearm L Forearm	+ ---	--- ---	7 years 5 years	Lesions healed primarily Lesions healed primarily
2007	Nagai MK, et al. [47]	M	R Lower Leg & Foot	+	---	Not stated	Amputation at 5 days
2008	Aslam M, et al. [48]	M	L Upper extremity	---	---	3 weeks	Thumb, black eschar
2008	Sinclair C, et al. [49]	F	R Arm & Hand	+	---	4 years	Amputation at 3 weeks
2010	Allen LM, et al. [50]	M	R Arm & Hand	+	---	Not stated	Contractures, wrist & hand
2010	Aydin U, et al. [51]	---	L Forearm & Hand	+	---	5 months	Deformed forearm & hand
2010	Khriesat WM, et al. [52]	M	R Forearm & Hand	+	---	2 years	Amputation at 20 Days
2012	Yurttutan S, et al. [53]	M	R Upper extremity	+	---	3 months	Healing skin graft

*Most articles have more than one author; see References.
--- Data absent
+ Photo present

intrinsic events or conditions.

Extrinsic (typically mechanical) causes include ischemia due to intrauterine fetal extremity malposition or compression (for example an extremity compressed between the fetal cranium and the maternal pelvic wall), blunt trauma or pressure to the mother's uterus, an abnormal birth canal, traumatic delivery, amniocentesis, prolapse of an extremity, and constricting bands around a limb of the fetus caused by the umbilical cord, amniotic bands, or placenta. Maternal hypertension, either preexisting or produced by excessive contractures of the womb during prolonged labor with maternal exhaustion, premature amniotic rupture sequence, oligohydramnios (dry labor) and polyhydramnios have also been proposed as causes of increased intrauterine pressure.

Intrinsic causes include congenital heart disease, vascular luminal occlusion due to insufficient development of fetal arterial or venous structures, prolonged vasospasm, or a hypercoagulable state leading to intra-arterial or intra-venous thromboses in either the mother or the fetus. Maternal hypercoagulopathy or actual emboli (originating from an infarcted placenta, most likely to occur with toxemia of pregnancy) may travel to the fetus. Fetal emboli may originate from inherited thrombophilia, congenital cardiac defects, renal or adrenal vein thrombosis, the umbilical arteries and veins, or the dying fetus, and embolize across the foramen ovale or through a patent ductus arteriosus. Some cases have been thought to be associated with fetal arterial spasm, disseminated intravascular coagulation, hyper viscosity syndrome, polycythemia, thrombocytopenia, decrease plasminogen activity, or methylenetetrahydrofolate reductase deficiency (MTHFR deficiency [45,52,53]).

Predisposing or accompanying conditions include maternal diabetes, gestational hypertension, excessive maternal weight gain, maternal lupus, first gestation in mothers younger than 25 years, prolonged gestation, delayed delivery, prolonged labor, premature labor, premature birth, spontaneous premature rupture of membranes, previous spontaneous abortions, birth asphyxia, fetal heart disease, fetal idiopathic cerebral infarction, fetal dehydration, and low birth weight.

In most cases, including the case presented, the etiology or pathogenesis is unknown. The need for multiple factors to act simultaneously may explain the rarity of the condition. Although intrauterine vascular insufficiency affecting a limb of a fetus may be precipitated by a wide variety of situations, and may be multifactorial, the end result is diminished tissue perfusion and local ischemia of the involved extremity, which can result in superficial and deep tissue necrosis, including the physis.

Treatment

The management of neonatal extremity gangrene is initially supportive and non-operative, preventing infection of the affected part, and allowing the gangrenous area to demarcate and slough spontaneously. Limb retention is a primary goal. Neonates have enormous potential to develop collateral circulation. However, there is a need to avoid systemic coagulopathy, systemic infection, and renal damage due to necrosis of the extremity [27,51]. Amelioration of some of the musculoskeletal complications may be possible by early recognition using pulse oximetry, arteriography or Doppler ultrasonography to facilitate thrombolytic therapy with heparin, streptokinase, or urokinase. Intra-arterial thrombectomy or embolectomy by catheter has been used successfully in isolated cases [19,21,25]. One case was "successfully treated" with a combination of recombinant tissue plasminogen activator, enoxaparin and collagenase application followed by surgery [53]. Compartment pressure measurements may help determine if fasciotomy, thrombectomy, embolectomy, or debridement of necrotic tissue is warranted [22,23,26,27,48,50]. MRI may reveal nonvascularized muscle groups [50]. Soft tissue debridement and skin grafting, or vacuum –assisted closure (VAC [57]) is indicated when no further improvement is anticipated. Since the line of demarcation tends to migrate distally, amputation should be delayed a long as possible [8,36,49,52], unless the overall health of the infant is jeopardized. Amputation should be designed to save growth plates if possible [42].

During recovery, early aggressive hand therapy and splinting

may be helpful to minimize functional deficit. Other than one case of surgical radial shortening to realign the hand [31], and a proposed staged surgical reconstruction of the limb [33], there have been no recorded attempts to treat subsequent bone relative shortening or angular deformity. For the first time, this paper recommends following each patient long enough to document physeal damage to determine if excision of a physeal bar or physeal bar equivalent is an option. If physeal abnormalities are identified the patient will need to be followed until maturity.

Discussion

This infant's vascular limb deficiency was present at birth (Figure 1), and by day 6 there were 3 separate and distinct areas of well-developed gangrene and one "white eschar" (Figure 2). This prompts two questions. First; were these four lesions the product of one or more separate intrauterine injuries? If the lesions were caused by limb trauma, such as impingement of the arm between the baby's skull and the mother's pelvis, there could indeed have been four separate traumatic events. Secondly; when did the vascular deficiency episodes occur? The smaller left forearm at birth, and the presence of the gangrenous lesions between day 1 and day 6 suggest that the vascular deficiency events began well before birth. No abnormalities were noted on the 12 and 20 week prenatal ultrasound studies. In the future, it is possible that improved technology and more frequent use of prenatal ultrasound studies may identify these lesions prior to birth.

This is the first report of intrauterine vascular insufficiency to show early comparison x-rays, and the earliest x-rays to show physeal abnormality (Figure 3A and B). The metaphyseal-physeal abnormalities at the distal humerus, proximal and distal radius, and distal ulna suggest complete physeal arrest, which subsequently manifested as deficient longitudinal bone growth and delayed epiphyseal ossification center development (Figure 5). The thumb metacarpal growth abnormality is a central physeal bar, while the index finger metacarpal growth abnormality is a typical physeal bar equivalent (death of a portion of the physis with no bone bridge between metaphysis and epiphysis) [1] (Figure 6). Each arrest produced relative shortening of the involved bone. Interestingly, the 3rd, 4th, and 5th metacarpals, and all phalangeal physes continue to remain open and growing. A slowly increasing cubitus valgus and mild wrist ulnar plus deformity may be due to closure of the proximal radial physis combined with growth of the proximal ulnar physis.

There is a significant volume of published literature on fracture-separation of epiphyses occurring during birth [56]. This occurs most commonly in the proximal and distal humerus. The time interval between fracture of the physis and radiographic identification of premature physeal arrest is usually weeks to months [56]. The time interval between a vascular insufficiency injury of the physis and radiographic identification of premature physeal arrest is usually months to years [57,58]

None of the literature in Table 1 followed patients adequately to challenge our statement that the patient presented here represents the youngest patient on record to have radiographically proven random ischemic physeal arrests. Thus, we would recommend that any child who survives intrauterine limb vascular insufficiency have physical examination and limb radiographic evaluation at birth and periodically thereafter until maturity, to search for premature partial physeal arrest distal to the site of the deficiency, and to determine if physeal bar or physeal bar equivalent excision is an option [1,56,59].

Summary

This case of intrauterine antenatal upper limb vascular insufficiency resulted in multiple random physeal arrests distal to the sites of vascular deficiency. The incidence of premature physeal arrest following vascular deficiency of a limb in utero is unknown, but is suspected to be high. The time interval between intrauterine vascular insufficiency and the discovery of a physeal arrest is also unknown, but like all previous cases of vascular deficiency from any cause, premature physeal arrest would be expected to become evident in months to years. This case suggests that all such cases be followed closely for several years in search of subsequent premature physeal arrest distal to the site of vascular deficiency. We suggest physical and radiographic evaluation at birth and periodically thereafter until maturity if a physeal abnormality is identified.

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