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Case Report

Comparative evaluation of radial ray defect associated with different syndromic conditions

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ABSTRACT

Radial ray defect (RRD) is a rare congenital anomaly resulting from abnormal development of the preaxial structures of the upper limb. It encompasses a spectrum of malformations ranging from radial hypoplasia to complete absence of the radius and associated radial-sided structures. Although RRD may occur as an isolated defect, it is frequently associated with syndromic conditions and multisystem congenital anomalies. Two male fetuses, aged 24 and 17 weeks of gestation, presenting with bilateral RRDs were examined by detailed external inspection, anatomical dissection, and radiography. In case 1, bilateral upper limb anomalies were associated with vertebral defects, anal atresia, oesophageal atresia, and bilateral cystic renal dysplasia. The left radius was absent, whereas the right radius was markedly shortened and associated with thumb aplasia. The constellation of anomalies was suggestive of the VACTERL association spectrum. In Case 2, bilateral RRDs were accompanied by craniofacial dysmorphism, including a square-shaped face, broad mandible, prominent forehead, broad nasal base, reduced nasal height, and low-set ears. The left radius was absent, whereas the right radius exhibited partial hypoplasia. The phenotypic features demonstrated overlap with Holt-Oram syndrome. These cases highlight the broad anatomical spectrum and syndromic variability of RRDs. Comprehensive anatomical, radiological, and fetal autopsy examinations are essential for accurate phenotypic characterization and recognition of associated malformations. Early prenatal detection using three-dimensional ultrasonography, combined with clinical genetic evaluation, can facilitate accurate diagnosis, parental counselling, and multidisciplinary management.

Keywords: Radial ray defect, VACTERL association, Holt-Oram syndrome, Fetal anatomy, Prenatal diagnosis

INTRODUCTION

The upper limbs develop from embryonic limb buds, which first appear as elevations on the anterolateral aspect of the body wall between days 26 and 30 of embryonic development.[1] Limb development involves initiation, growth, and patterning along the proximodistal, anteroposterior, and dorsoventral axes. These processes are tightly regulated through a balance between cellular proliferation and programmed cell death.[1] Limb bud formation and elongation are driven by rapid cell proliferation within the progress zone (PZ), under the influence of the overlying apical ectodermal ridge (AER). Proximodistal growth is closely coordinated with anteroposterior patterning, regulated by the zone of polarizing activity (ZPA), and dorsoventral patterning, which collectively ensure normal limb morphogenesis.[2]

The radial ray is the embryonic precursor of the radius, scaphoid, trapezium, first metacarpal, and the two phalanges of the thumb. RRD is a rare congenital anomaly with an estimated incidence of approximately 1 in 30,000 live births.[3,4] A slightly higher prevalence has been

reported in males.[5] RRD encompasses a broad spectrum of anomalies ranging from hypoplasia to complete absence of the radius and associated radial-sided structures. Defects in radial ray development may result in varying degrees of defect involving not only skeletal components but also adjacent joints, muscles, tendons, ligaments, nerves, and blood vessels.[6]

Although RRD may occur as an isolated anomaly, accounting for approximately 8-30% of cases, the majority are associated with additional congenital abnormalities or syndromic conditions.[7] These include chromosomal disorders such as trisomy 13, trisomy 18, and 22q11.2 deletion syndrome, as well as associations and syndromes including VACTERL association, Fanconi anaemia, Holt-Oram syndrome, and thrombocytopenia with absent radius (TAR) syndrome.[7-12] RRDs therefore represent a heterogeneous group of disorders with diverse genetic and developmental etiologies. Most cases are unilateral and sporadic, whereas bilateral involvement is more frequently associated with multiple congenital anomaly syndromes.[13]

Prenatal identification of RRDs by ultrasonography presents a significant diagnostic challenge because the anomaly may occur in isolation or as part of chromosomal abnormalities, teratogenic exposure, skeletal dysplasias, or more than 200 recognized genetic syndromes. Particular attention should be directed toward evaluation of the hand, as abnormalities of the radius are frequently associated with thumb hypoplasia, shortening, or aplasia. Assessment of the number, morphology, and arrangement of the digits is therefore crucial for accurate diagnosis and syndrome characterization.

The present study describes the anatomical manifestations of RRD in two cases associated with different syndromic conditions and highlights the importance of recognizing syndromic variability in congenital upper-limb anomalies.

CASE REPORT

Two male fetuses with upper limb anomalies, aged 24 and 17 weeks of gestation, were obtained from the Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences (RIMS), Imphal, following approval from the appropriate institutional authorities. Detailed external examination, anatomical dissection, and radiological evaluation were performed in the Departments of Anatomy and Radiology, RIMS, Imphal.

Case 1

External examination revealed bilateral upper limb deformities. The left upper limb showed abnormal radial deviation of the wrist with lateral rotation of the hand, accompanied by absence of the thumb and index finger. The right upper limb demonstrated abnormal wrist angulation with medial rotation of the hand and aplasia of the thumb. Additional external anomalies included bilateral rocker-bottom feet and anal atresia (Figure 1 a and b).

On dissection, the right radius was markedly shortened, and the ulna exhibited medial curvature around the radius. On the left side, the radius was completely absent, leaving an isolated ulna. Skeletal examination of the left hand revealed absence of the first and second metacarpals, together with absence of the corresponding phalanges of the thumb and index finger. In the right hand, the first metacarpal and phalanges of the thumb were absent.

Internal examination demonstrated isolated oesophageal atresia without an associated tracheoesophageal fistula (Figure 2 a and b). Both kidneys were poorly developed and exhibited features of bilateral cystic renal dysplasia (Figure 2 d). No gross abnormalities were identified in the heart or umbilical cord.

Radiographic evaluation confirmed shortening of the right radius with compensatory curvature of the ulna (Figure 1 c). Complete absence of the left radius and preservation of an isolated ulna were noted (Figure 1 d). The first and second metacarpals and the phalanges of the thumb and index finger were absent in the left hand. Computed tomography (CT) further revealed wedge-shaped vertebral anomalies involving the thoracic and lumbar vertebrae (Figure 1 e).

Case 2

External examination revealed multiple craniofacial and upper limb anomalies. The fetus exhibited a square-shaped face, prominent forehead, broad mandible, and a broad-based nose (Figure 3 a). The nasal width measured 6 mm, while the nasal height measured 8 mm. Low-set ears and a cervical hump were also present (Figure 3 b).

The left upper limb showed abnormal angulation of the wrist with medial rotation of the hand, absence of the thumb, and partial syndactyly between the index and middle fingers. The right upper limb demonstrated abnormal wrist angulation, with absence of both the thumb and index finger.

Dissection revealed complete absence of the left radius, resulting in an isolated ulna (Figure 3 c). Only three metacarpal bones were present in the left hand. On the right side, the radius was partially developed; the proximal segment appeared relatively normal, whereas the distal segment was markedly hypoplastic and represented only by a fibrous cord-like structure (Figure 3 d). Consequently, the wrist joint lacked adequate skeletal support. No cardiac malformations or other major visceral anomalies were identified during internal examination.

Radiological evaluation, including plain radiography and three-dimensional computed tomography (3D-CT), confirmed complete absence of the left radius and partial hypoplasia of the right radius (Figure 3 c).

Table 1: Limb findings, type and laterality.

Cases	1		2	
	Left	**Right**	**Left**	**Right**
Radius	Absent	Short	Absent	Present
Ulna	Present	Present and bend sideways	Present	Present
Fingers	Thumb and index finger were absent	Thumb absent	Thumb absent, index and middle finger partially fused	Thumb and index finger were absent
Type	Type IV	Type II	Type IV	Type I
Laterality	Bilateral		Bilateral	

Table 2: Associated findings.

Vertebrae	Wedged-shaped vertebrae	Normal vertebrae
Umbilicus	Normal	Normal
Anus	Imperforated	Normal
Esophagus	Oesophagal atresia without tracheoesophageal fistula	Normal
Kidney	Bilateral cystic renal dysplasia	Normal
Heart	Normal	Normal
Facial anomalies	-	+++
Gestational age	24 weeks	17 weeks
Laterality	Bilateral	Bilateral
Final analysis	VACTERL association	Likely Holt-Oram syndrome

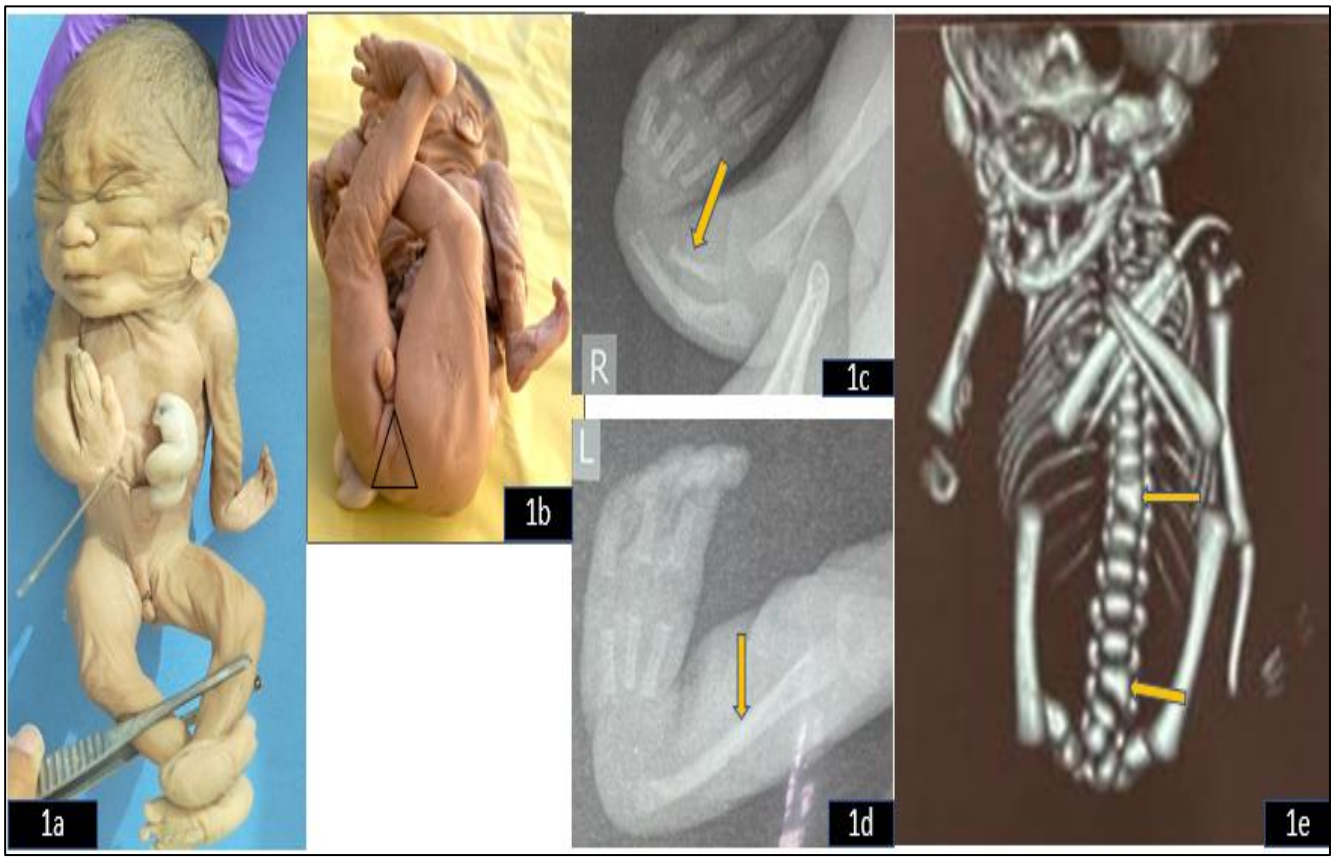

Figure 1 (a-e): Gross and radiological examination of (a) case 1; (b) imperforated anal orifice, (c) short radius, right, (d) isolated left ulna, (e) CT image showing Wedge shape vertebrae.

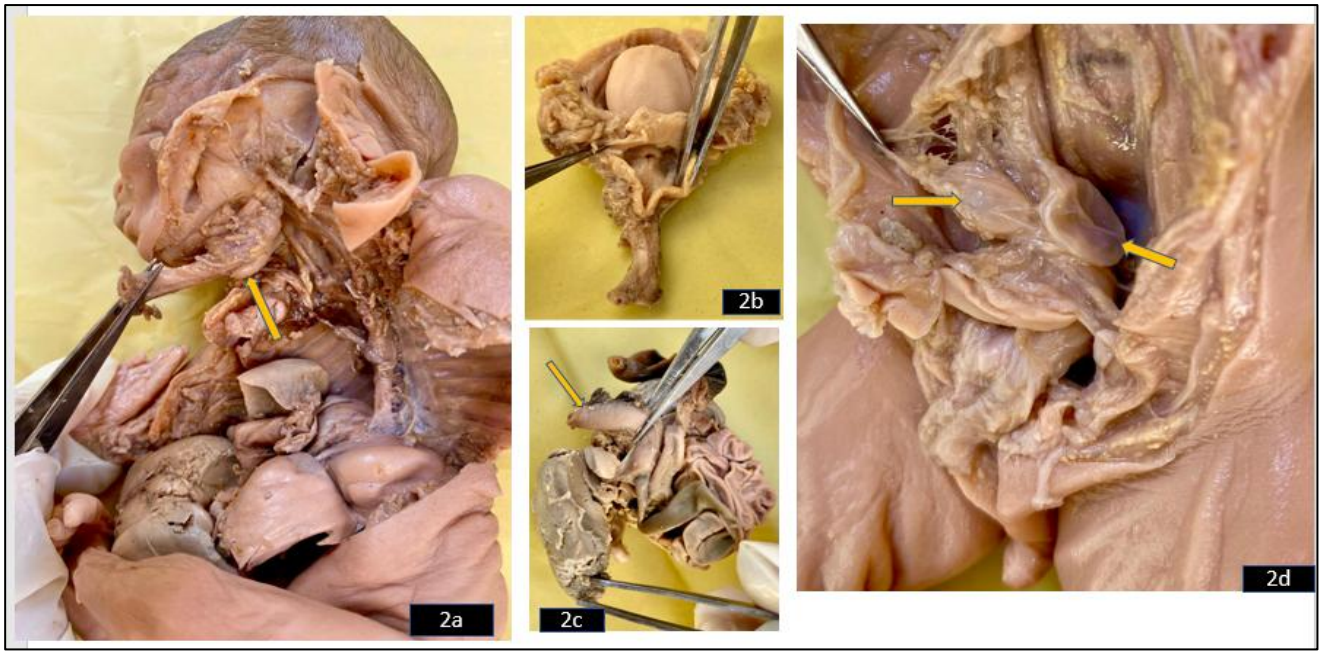

Figure 2 (a-d): Internal examination of case 1; (a) esophageal atresia, (b) blind end of esophagus, (c) blind cardiac end of stomach and (d) cystic renal dysplasia.

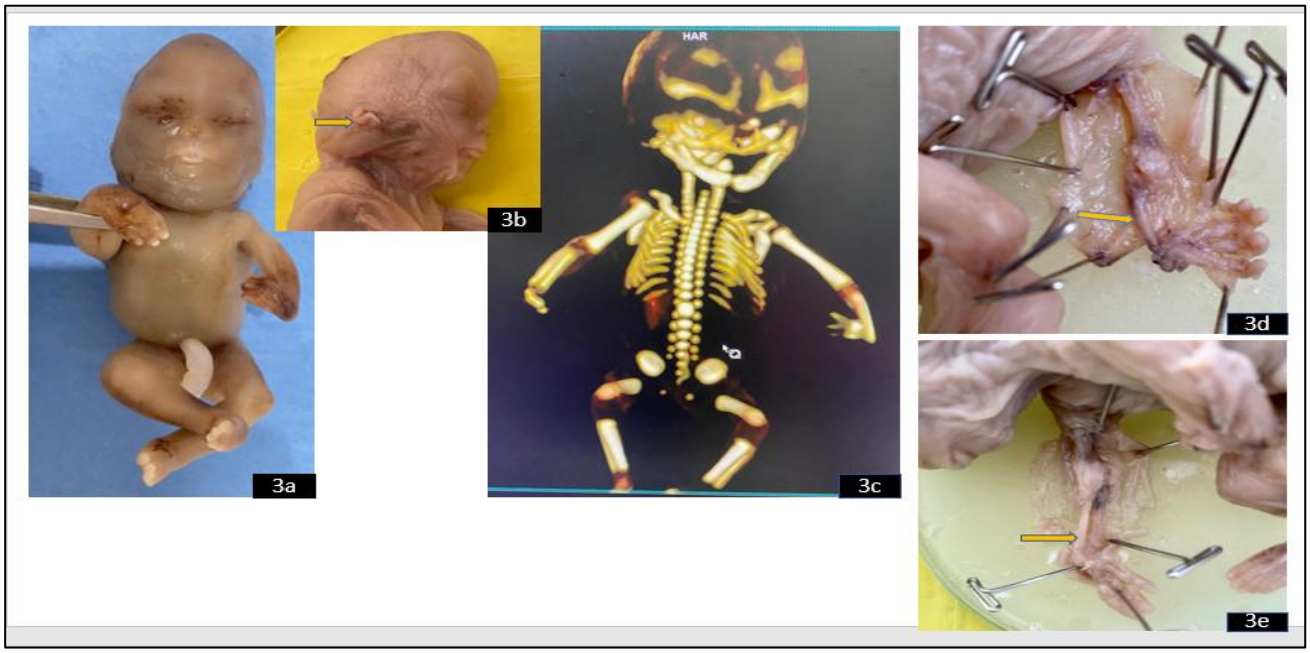

Figure 3 (a-e): Gross and radiological examination of (a) case 2; (b) low set ear; (c) isolated left ulna; (d and e) fibrous cord like distal part of radius.

DISCUSSION

RRD represents a rare spectrum of congenital upper limb malformations resulting from abnormal development of the preaxial structures of the upper limb. The severity of involvement ranges from mild radial hypoplasia to complete absence of the radius and associated radial-sided structures. Bilateral involvement is uncommon and is more frequently associated with syndromic conditions or multiple congenital anomalies than unilateral defects.[2,13,15]

Both fetuses in the present study exhibited bilateral radial ray anomalies accompanied by additional congenital malformations, suggesting an underlying syndromic etiology.

The first case demonstrated a constellation of anomalies including bilateral RRDs, anal atresia, oesophageal atresia, renal dysplasia, and vertebral abnormalities. These findings are consistent with the diagnostic spectrum of VACTERL association, which is characterized by the non-

random occurrence of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula with or without oesophageal atresia, renal anomalies, and limb abnormalities.[15-18] The diagnosis of VACTERL association is generally considered when at least three component anomalies are present.[15,16] In the present case, vertebral, anal, oesophageal, renal, and limb abnormalities were identified, thereby fulfilling the commonly accepted diagnostic criteria. Vertebral defects have been reported in approximately 60-80% of patients with VACTERL association, while anal atresia and limb abnormalities occur in 55-90% and 40-50% of affected individuals, respectively.[17,18] The combination of anomalies observed in case 1 therefore strongly supports a diagnosis within the VACTERL spectrum.

The second case presented with bilateral radial ray anomalies associated with distinctive craniofacial features, including a square-shaped face, broad mandible, prominent forehead, broad nasal base, reduced nasal height, and low-set ears. The upper limb abnormalities consisted of complete absence of the left radius, hypoplasia of the right radius, thumb aplasia, and digital anomalies. These findings showed similarities to phenotypic features reported in Holt-Oram syndrome, an autosomal dominant disorder characterized primarily by upper limb malformations and cardiovascular abnormalities.[19] Upper limb defects in Holt-Oram syndrome vary considerably and may include absent or hypoplastic thumbs, abnormalities of the first metacarpal, and hypoplasia or aplasia of the radius.[19]

Although facial dysmorphism is not considered a classical feature of Holt-Oram syndrome, several reports have described patients presenting with associated craniofacial abnormalities, including prominent forehead, hypertelorism, depressed nasal bridge, low-set ears, and mandibular asymmetry.[22] The craniofacial characteristics observed in the present case overlap with some of these reported features. Similar facial anomalies associated with a RRD have also been reported, including a square-shaped face, broad lower jaw, tall and prominent forehead, hypertelorism, wide-based nose, reduced nasal height, and low-set ears.[23] Furthermore, anthropometric studies have demonstrated that reduced nasal height and increased nasal width may contribute to the distinctive facial appearance observed in certain syndromic conditions.[21,23] In a study of the Manipuri fetal population in the group of 17-20 weeks of gestation, the mean nasal height and nasal width were reported as 10.4±1.8 mm and 5.5±1.1 mm, respectively.[23] In the present fetus, the measured nasal height (8 mm) was lower than the reported mean, whereas the nasal width (6 mm) was relatively increased, supporting the presence of facial dysmorphism. However, in the absence of cardiac abnormalities and molecular genetic confirmation, the diagnosis of Holt–Oram syndrome should be considered presumptive rather than definitive.

Thrombocytopenia with absent radius (TAR) syndrome was considered in the differential diagnosis because radial aplasia is a characteristic feature of the disorder. However, TAR syndrome is typically distinguished by bilateral absence of the radius with preservation of the thumbs, which are usually present although often hypoplastic.[5,24] In contrast, both fetuses in the present study exhibited thumb aplasia. Moreover, no lower limb abnormalities suggestive of TAR syndrome were identified. Therefore, the observed pattern of anomalies is not consistent with a diagnosis of TAR syndrome.

RRD are commonly classified into four types according to the severity of radial involvement. Type I is characterized by mild shortening of the radius with minimal wrist deviation; type II by a markedly shortened radius and radial deviation of the wrist; type III by partial absence of the radius; and type IV by complete absence of the radius.[25] Based on this classification, the left upper limbs of both fetuses corresponded to Type IV RRD because of complete radial aplasia. The right upper limb in case 1 was consistent with type II RRD, as the radius was shortened and associated with ulnar bowing and wrist deformity. The right upper limb in Case 2 demonstrated partial radial development with distal hypoplasia and may be classified as type I RRD.

The embryological basis of RRD is complex and involves disruption of molecular pathways responsible for limb bud initiation, outgrowth, and patterning. Limb development is regulated by interactions among several signaling centers and transcription factors, including fibroblast growth factors (FGFs), wingless-related integration site (WNT) proteins, bone morphogenetic proteins (BMPs), HOX genes, and T-box transcription factors.[26] TBX5 plays a critical role in upper limb specification, and mutations in this gene are responsible for Holt-Oram syndrome. Similarly, mutations in SALL4 and other developmental genes have been implicated in radial ray malformations.[26] Disruption of these signaling pathways during early limb morphogenesis may result in varying degrees of radial defect and associated anomalies affecting other organ systems.

A male predominance has been reported in RRD, with an estimated male-to-female ratio of approximately 3:2.[5] Both fetuses in the present study were male, which is consistent with previous observations. The occurrence of bilateral RRDs in association with multiple congenital anomalies highlights the importance of comprehensive anatomical and radiological evaluation. Such examinations facilitate accurate phenotypic characterization, aid in the recognition of syndromic associations, and contribute to a better understanding of the developmental mechanisms underlying these rare congenital malformations.

Based on the observed morphological features, case 1 most closely resembles the VACTERL association spectrum, whereas case 2 demonstrates features suggestive of a radial ray syndrome with phenotypic overlap with Holt-Oram syndrome. Nevertheless, definitive syndromic

classification would require genetic and molecular investigations, which were not available in present study.

CONCLUSION

RRD is a rare spectrum of congenital upper limb anomalies that may occur as an isolated defect or, more commonly, in association with multiple congenital malformations and syndromic disorders. Clinicians should suspect RRD when prenatal or postnatal evaluation reveals radial shortening or aplasia, abnormal angulation of the wrist, thumb hypoplasia, or thumb aplasia.

The two cases presented demonstrated the diverse anatomical manifestations of RRD and highlighted its association with complex multisystem anomalies. The findings underscore the importance of comprehensive anatomical dissection, radiological evaluation, and fetal autopsy in accurately characterizing the extent of skeletal and visceral involvement. Such detailed assessment aids in identifying underlying syndromic associations and enhances understanding of the embryological basis of these malformations.

From a clinical perspective, recognition of the anatomical spectrum of RRD is important for anatomists, radiologists, obstetricians, pediatricians, orthopedic surgeons, and clinical geneticists. Advances in prenatal imaging, particularly three-dimensional ultrasonography (3D-USG), have improved the early detection of radial ray anomalies during gestation. Integration of detailed prenatal imaging with clinical genetic evaluation can facilitate accurate diagnosis, appropriate parental counselling, and long-term management planning for affected individuals.

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