

Majewski syndrome, Short Rib Polydactyly Syndrome (SRPS) Type II - A rare case report, with review of literature

ABSTRACT

Short Rib Polydactyly Syndrome (SRPS) type II also known as Majewski syndrome, is the rarest of the four subtypes of SRPS which is a rare inherited skeletal dysplasia. We report a case of Majewski syndrome in a neonate with brief review of literature.

A 24 years old primigravida, with history of second degree consanguineous marriage underwent a Prenatal USG which revealed anhydramnios, bilateral enlarged kidneys, extremely narrow thorax and bilateral short limbs with polydactyly. Based on these findings a probable diagnosis of lethal skeletal dysplasia was made and termination of pregnancy advised. Refusing termination the mother delivered a male foetus at 30weeks with severe respiratory distress and gross anomalies. The foetus succumbed to respiratory failure inspite of resuscitation. Gross findings were a male foetus with enlarged head, hydropic face, hypertelorism, short nose, depressed nasal bridge, pseudo cleft lip, cleft palate, low set posterior rotated ears, cystic hygroma, micrognathia, short and narrow chest, all the limbs showed mesomelic limb shortening, postaxial polydactyly, syndactyly and brachydactyly. Postnatal X-ray, CT scan and USG confirmed the above mentioned features and additional findings were extremely short horizontal ribs and disproportionately shortened ovoid tibia.

Autopsy revealed a bell shaped thorax, small hypoplastic lungs, bilateral enlarged kidneys, atrial septal defect, hypoplastic epiglottis and larynx and short small intestine. Microscopic findings of pulmonary hypoplasia, renal cystic dysplasia, hepatic fibrosis and markedly retarded endochondral ossification correlate with the clinical, radiological and pathological findings of Short Rib Polydactyly Syndrome Type II -Majewski Syndrome.

Keywords: Short Rib Polydactyly Syndrome Type II, Majewski Syndrome

1. INTRODUCTION

Short rib-polydactyly syndromes (SRPS) are a heterogeneous group of recessively inherited lethal osteochondrodysplasias, the prevalence rate is reported to be about 2.1 to 2.3/10,000 births and the rate of lethal osteochondrodysplasia is about 0.95/10,000 births.¹ There are four classical subtypes of SRPS with a common finding of small and narrow thorax with short ribs and hypoplastic lungs alongwith pre/postaxial polydactyly. Apart from these findings in all the four subtypes, Type I - Saldino-Noonan is characterized by severely shortened flipper like extremities, polycystic kidneys and pointed metaphyses, Type II- Majewski is characterized by cleft lip, cleft palate, epiglottis/laryngeal hypoplasia, renal cystic disease and short, ovoid tibia, Type III -Verma-Naumoff is characterized by extreme micromelia with severely dysplastic widened metaphyses and occasionally situs inversus, Type IV -Beemer-Langer is characterized by extreme micromelia with smooth metaphyseal margins, macrocephaly with frontal bossing, cleft lip, cleft palate and CNS abnormalities.

We report a case of SRPS type II – Majewski syndrome; the rarest out of the 4 types of SRPS, which itself is an extremely rare group of syndromes with less than 100 published cases in the literature.²

The aim of this case report is to inform some unique findings like short small intestine, hypoplastic epiglottis and larynx, hepatic fibrosis and atrial septal defect which have either not been reported or very rarely reported in the past with Majewski syndrome along with clinical, radiological and histopathological features.

2. PRESENTATION OF CASE

Pregnancy history- A 24 years old primigravida with a history of consanguinity was antenatally diagnosed with anhydramnios and multiple congenital fetal anomalies on USG scan at 28 weeks of gestation.

Prenatal Ultrasonographic findings- a single live intrauterine fetus with bilateral echogenic enlarged kidneys, minimal fetal ascites, bilateral short limbs and anhydramnios. Based on these findings a probable diagnosis of a lethal skeletal dysplasia was made and termination of pregnancy advised, which the mother refused.

Birth and Perinatal history -A male neonate was delivered by normal delivery at 30weeks of gestation with severe respiratory distress and gross anomalies. The foetus did not cry immediately after birth. His heart rate was 60/min, no spontaneous respiration, the 1min APGAR score was 2, the 5 min APGAR score was 2, after which CPR was given. The neonate succumbed to respiratory failure in spite of resuscitation and was sent for perinatal autopsy.

External examination- A male neonate with attached umbilical cord, without placenta and weighing 1.9kgs was received. All external orifices were patent. Significant anthropometric findings were an increased upper segment: lower segment ratio of 2.5:1(normal for the age is 1.7:1), arm span of 30cms (normal = 2-3cms less than total length) and a total length of 43cms, which suggested short limb short stature. Also noted were a decreased chest circumference and an increased abdominal circumference.

Postnatal Imaging studies- X-ray and CT scan- revealed extremely short horizontal ribs, normal pelvis and vertebrae, extreme micromelia, disproportionately shortened ovoid tibia and postaxial polydactyly in all four limbs (Figure-I). USG- abdomen- showed bilateral enlarged kidneys.

Autopsy findings- external examination of the neonate revealed macrocephaly, a prominent forehead, hydropic facies, hypertelorism, short nose, depressed nasal bridge, pseudocleft lip, extremely short and narrow chest, protuberant abdomen and hypospadias (Figure-II). Additional findings were a cleft palate, posteriorly rotated low set ears, micrognathia and cystic hygroma (Figure-III). All four limbs showed micromelia, mesomelic limb shortening, postaxial polydactyly, syndactyly, brachydactyly and nail dysplasia (Figure-IV). Internal examination revealed short, horizontal ribs and a characteristic bell shaped thorax. Gross findings were extremely small bilateral hypoplastic lungs i.e. 20gms/1900gms= 0.0105 (normal > 0.015) and bilateral enlarged kidneys. Additional findings were an atrial septal defect, short small intestine i.e. 90cms in length (normal >200cms), hypoplastic epiglottis and larynx. Microscopically bilateral pulmonary hypoplasia was noted, which is assessed by drawing a perpendicular line from a terminal bronchiole to the pleura. The line should contain <5 alveolar spaces within to call it pulmonary hypoplasia (Figure-V-A). Sections from tibial metaphyses and costochondral junction showed markedly retarded endochondral ossification with chondrocytes in the growth zone markedly reduced in number and disorderly arranged (Figure-V-B). Liver showed band like periportal fibrosis and extramedullary haematopoiesis (Figure-V-C). Bilateral kidneys showed microcystic spaces, premature collecting ducts, immature mesenchyme, dysplastic changes, cystic dilatation of the tubules both in the cortex and medulla; occasional glomeruli in the cortex also showed cystic dilatation (Figure-V-D). All other organs were normal grossly with normal histology.

Hence, based on these radiological, clinical and pathological findings a diagnosis of Short Rib Polydactyly Syndrome type II- Majewski Syndrome was made.

The inability to do chorionic villous sampling, amniocentesis and chromosomal analysis was due to limitations in the diagnostic facilities available.

3. DISCUSSION

Majewski syndrome was first described in 1971 by Majewski et al, which was later labelled as Short Rib Polydactyly Syndrome (SRPS) type II - Majewski syndrome. They described 4 newborn babies dying shortly after birth who exhibited severe malformations including median cleft lip, polysyndactyly, short ribs and limbs, genital abnormalities, and anomalies of epiglottis and visceral organs. [3] All of the features described were seen in our case along with some additional findings such as short ovoid tibias, hydrops fetalis, hypertelorism, low set posteriorly rotated ears, broad flat nose, bell shaped thorax, protuberant abdomen, hypoplastic lungs, renal cystic dysplasia, atrial septal defect, hepatic fibrosis and retarded endochondral ossification.

Constant clinical findings seen in all cases of Majewski syndrome are extremely short limbs with pre/postaxial polydactyly of the hands and feet, small/narrow chest with short ribs and pulmonary hypoplasia, protuberant abdomen, median cleft lip or pseudo-cleft of the upper and lower lip or cleft palate, epiglottis and larynx hypoplasia, short/ovoid tibias with round ends, presence of premature ossification centers and early neonatal death. Some of the common findings include polyhydramnios, hydrops fetalis, ocular hypertelorism, broad and flat nose, low-set ears, ambiguous genitalia and renal cystic disease. Other findings which can occasionally be seen in these cases are short small intestine, malrotation of the bowel, cardiac malformations and dysplastic pancreas. Radiographic findings are extreme micromelia with smooth rounded metaphyses, extremely short horizontal ribs, normal pelvis and vertebrae, disproportionately shortened ovoid-

shaped tibiae, pre- and post-axial polydactyly, syndactyly, brachydactyly and advanced skeletal ossification—advanced maturation of the proximal femora and humeri. Histopathological findings are markedly retarded endochondral ossification i.e. the chondrocytes in the physal growth zones are markedly reduced in number and disorderly arranged. Lungs show hypoplasia with abnormally small size and low weight. ^[4] The present case demonstrated all of the constant clinical findings and most of the common and occasional clinical findings, radiological findings and all of the histopathological findings of SRPS type II – Majewski syndrome.

Padmini et al reported a case of Majewski syndrome with features of a bulging forehead, depressed nasal bridge, low set ears, cleft lip, narrow thorax, polydactyly, rudiment of phallus, undescended testes, hypoplastic lungs, vertebral anomalies, anal atresia, trachea-esophageal fistula, esophageal atresia and renal anomalies. ^[5] Our case demonstrated most of these features except the genital abnormalities mentioned in this case. Anal atresia, tracheoesophageal fistula and esophageal atresia are the features commonly seen in Type I SRPS rather than Type II where they are seen only occasionally. The differences between the 4 types of SRPS and the features seen in the present case are shown in Table-I. ^[4]

Phenotypically an important differential diagnosis for Majewski syndrome is Mohr syndrome which was reported by Silengo et al who discussed two cases that presented with laryngeal anomalies, and hallucal and postaxial polysyndactyly of the feet. These rare malformations are also seen in Majewski syndrome. Other features of Mohr syndrome which help differentiate the two entities are a lobate tongue with papilliform protuberances, angular form of alveolar process of the mandible, supernumerary sutures in the skull, and an episodic neuromuscular disturbance. ^[6] SRPS should be differentiated from other skeletal dysplasias presenting with micromelia and thoracic hypoplasia namely achondrogenesis, thanatophoric dysplasia, hypophosphatasia, and osteogenesis imperfecta type 2. However, postaxial polydactyly is present only in SRPS, while hypomineralization is only rarely present in some subtypes of SRPS. Another condition to be distinguished from SRPS is chondroectodermal dysplasia (Ellis-van Creveld syndrome), in which thoracic hypoplasia is less pronounced and the limbs are less affected. ^[7]

By genomewide linkage and homozygosity mapping in 2 consanguineous families of Majewski syndrome, Thiel et al mapped the disorder to chromosome 4q32.1-q34.3. C.P Chen et al reported that SRPS has been found to be caused by mutations in the genes of IFT80, DYNC2H1, NEK1 or WDR35. ^[8] El Hokayem et al reviewed the clinical features of 11 cases of Majewski syndrome, 4 of which were due to mutations in the NEK1 gene, 4 due to mutations in the DYNC2H1 gene and in 3 cases, no mutation was detected in either gene. Lingual and gingival hamartoma were frequently observed in the mutation-positive group, present in 60% of NEK1 cases and 25% of DYNC2H1 cases. Lobulated tongue, holoprosencephaly and polymicrogyria were mostly observed in the mutation-negative group. Kidney cysts, intestinal malrotation and heart defects were observed in both groups. ^[9]

Since, all SRPS have an autosomal recessive inheritance pattern there is a 25% recurrence rate. Therefore, in case of termination of pregnancy after ultrasonographic diagnosis, confirmation by autopsy is of utmost importance. When a correct diagnosis is made, it can be followed up by genetic counseling and early ultrasound monitoring of the next pregnancy.

4. CONCLUSION

In conclusion, the present case report draws attention to the various aspects of diagnosing SRPS type II- Majewski syndrome from the clinical, radiological and histopathological aspects. As the condition is invariably fatal during the neonatal period, the antenatal diagnosis is very important. Termination of pregnancy regardless of the period of gestation and genetic counseling for recurrence risk after confirmation of the diagnosis is advised.

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136 **CONSENT (WHERE EVER APPLICABLE)**
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138 "All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for
139 publication of this case report and accompanying images. A copy of the written consent is available for review by the
140 Editorial office/Chief Editor/Editorial Board members of this journal."
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143 **ETHICAL APPROVAL (WHERE EVER APPLICABLE)**
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145 Informed consent was taken from the neonate's parents before conducting the autopsy and all measures have been taken
146 to protect the privacy of the subject.
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174 **TABLE- I**

175 **Comparative study of the four types of Short Rib Polydactyly Syndromes and the present case**

SRPS	TYPE- I	TYPE- II	TYPE- III	TYPE- IV	PRESENT CASE (2015) TYPE- II
SHORT HORIZONTAL RIBS	+	+	+	+	+
SHORT LIMBS	+	+	+	+	+
PRE/POST AXIAL POLYDACTYLY	+	+	+	+/-	+
ABNORMAL VERTEBRAL BODIES	+	-	+	+	-
ABNORMAL ILIA	+	-	+	+	-
SHORT OVAL TIBIA	-	+	-	-	+
SMOOTH METAPHYSES	-	+	+	+	+
HYDROPS FETALIS	+	+	+	+	+
POLYHYDRAMNIOS	-	+	-	-	-
CLEFT LIP/PALATE	+	+	-	+	+
HYPOPLASTIC EPIGLOTTIS/LARYNX	-	+	+	-	+
HYPERTELORISM	-	+	-	+	+
BROAD FLAT NOSE	-	+	+	+	+
LOW SET EARS	-	+	-	-	+
GENITAL ABNORMALITIES	+	+	+	-	+
CNS ABNORMALITIES	+	-	-	+	-
SITUS INVERSUS	-	+	+	-	-

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FIGURES



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Figure I- Whole body CT scan- shows extremely short horizontal ribs, extreme micromelia, disproportionately shortened ovoid shaped tibiae and polydactyly.



Figure II- Neonate with hydrops, macrocephaly, hypertelorism, pseudocleft lip, extremely short&narrow chest, protuberant abdomen& short limbs with syndactyly



Figure III- Posteriorly rotated low-set ears, micrognathia, cystic hygroma and cleft palate



Figure IV- All four limbs of the neonate show postaxial polydactyly, brachydactyly, syndactyly and nail hypoplasia

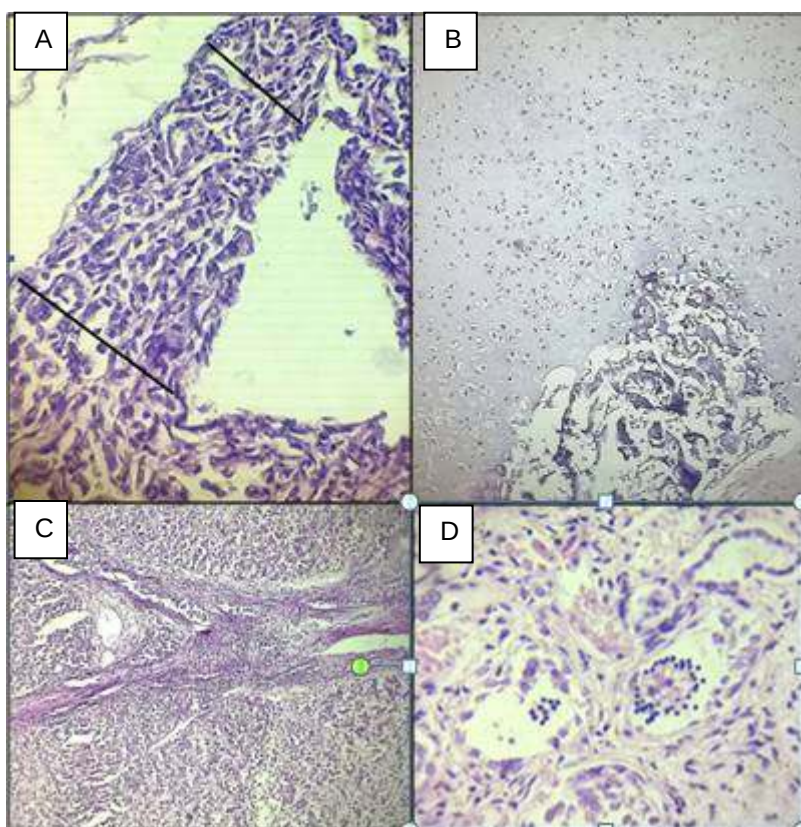


Figure V- A) Photomicrograph of lung-H&E x400 show pulmonary hypoplasia, which is assessed by drawing a perpendicular line from a terminal bronchiole to the pleura. The line should contain <5 alveolar spaces within to call it pulmonary hypoplasia, B) Photomicrograph of the Costochondral junction-H&E x100- Markedly retarded endochondral ossification with chondrocytes in the growth zone markedly reduced in number and disorderly arranged, C)

199 **Photomicrograph of Liver-H&E x400-Periportal fibrosis, D) Photomicrograph of Kidneys-H&E x400-Renal cysts&primitive**
200 **glomeruli.**