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Primordial Dwarfism: Report of seven cases; the first Case Series in Iran and Review of the literatures

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Abstract

Background: Primordial dwarfism is a rare group of genetic disorders that characterized by intra uterine growth retardation, short stature at birth and growth deficiency that persists throughout life. This disorder caused by various mechanisms such as chromosomal abnormalities, molecular changes and mutation of genes that result in developmental defects, facial dysmorphism and skeletal abnormalities in fetus. Primordial dwarfism includes of five specific subtypes that definitions vary from one type to another.

Objective: The aim of this study was to report of seven cases of Primordial dwarfism as the first Case Series in Iran and review of the literatures about the disorder.

Methods: This study has accomplished to have an overview of our PD patients and summarizes clinical findings of seven cases presented with severe growth retardation and clinical findings of this disorder that had no explain with other disorders, who referred to our department (Pediatric endocrine wards, Imam Reza Hospital) from June.2016 to September .2017. We also conducted a literature review about primordial dwarfism on Google scholar and Medline in PubMed area to compare our results with other reports.

Results: During the study period seven patients (5females and 2 males) between the ages of 18 months and 12 years old were identified. The most prevalent referring symptoms were growth retardation that presented in all cases. Other clinical signs and symptoms were included intrauterine growth retardation, low birth weight, specific clinical features such as microcephaly, narrow face, high pitch voice, prominent nose and other than that .Biochemical and imaging studies were done to rule out other diseases that can make growth retardation. The diagnosis of Primordial Dwarfism found due to clinical aspects.

Conclusions: This review will provide an overview of the clinical aspects and different subtypes of primordial dwarfism disorder and help to clinicians to have an attention to it for diagnose and further evaluations**.**

Keyword: Primordial dwarfism, Microcephaly, Subtypes, Clinical findings

Introduction

Primordial dwarfism (PD) is a group of disorders with significant prenatal and postnatal growth retardation and various clinical abnormalities that differ from one type to another (1). PD characterized by intrauterine growth retardation, low birth weight, small bones and body organs for gestational age (SGA). Female and male patients affect equally and they look smaller in size (weight and height) than normal individuals (2).

The major characteristic feature of PD that makes this disorder different from other forms of dwarfism is reduction in head size in proportion to or smaller than body and named as "micro cephalic primordial dwarfism". There is only one subtype of PD with normal head size called Russell-Silver Syndrome. Other clinical findings vary from a subtype to another. Many factors can contribute to result in PD that can divide into molecular, genetic and chromosomal changes (3).

PD is a rare heterogeneous condition and diagnostic category including specific features in 5 major subtypes. The main feature in all subtypes is prenatal and postnatal growth retardation. Patients are very small for their age and sex. They have diagnosed with intrauterine growth retardation (IUGR) and often have premature delivery and low birth weight (SGA). Growth delay continues after birth (1). Five subtypes in primordial dwarfism included: Seckel syndrome, Majewski osteodysplastic primordial dwarfism (MOPD type. I/III), MOPD type II, Meier-Gorlin syndrome and Russell- Silver –Syndrome (1). Russell silver syndrome is a specific group that patients have normal head size, other types has microcephaly (3). Seckel syndrome (SS) is a rare autosomal recessive disorder (4) and first defined by seckel in 1960. He described two cases of his study and 13 cases in the literatures over a 200 years period that characterized by sever microcephaly, large beaked nose, mild to moderate mental retardation and called it bird- headed dwarfism (5). In 1982, Majewski et al reported a term of osteodysplastic primordial dwarfism from reviewing some literatures and classified it in three categories with growth and mental retardation, bony anomalies and specific radiologic findings (6) Russell silver syndrome first reported by Russell and silver in 1950 and 1960 S. The characteristic features are low birth weight, short stature, body asymmetry and normal head size (1).

Meier-Gorlin syndrome or ear, patellae, short stature syndrome is another type of PD that is autosomal recessive disorder. First time in 1959 Meier et al described a case with micrognathia, microtia, absent patellae and cryptorchidism (7). Further clinical diagnostic features of these subtypes have presented in Table 1. In our article we present on 7patients that have different clinical presentations of this disorder, all of them had growth retardation from birth time and after that, other clinical features that helped us to diagnose this disorder describe as below. The aim of this study was have a presentation of this disorder in our country with its different types for the first time. We couldn't use genetic samples in our cases because of limitation in genetic assay in our country and expenses. We present these cases with their clinical features as a first time for introduce primordial dwarfism and make an attention for clinicians and other health care groups.

Table 1. **Subtypes of Primordial dwarfism and their corresponding clinical features**	
Primordial dwarfism subtypes	**Clinical features**
Seckel Syndrome	Sever microcephaly, narrow face, large beaked nose, receding mandible, micrognathia, low set ear, dental anomalies and clinodactyly.
MOPD type I/III	Microcephaly, bone dysplasia, dry skin, thinness in skull hair and eyebrows and bone anomalies.
MOPD type II	Microcephaly, prominent nose and eyes and narrow face, microdontia or missing teeth, skeletal anomalies, abnormal pigmentary changes and squeaky voice.
Russell-silver syndrome	Small triangular face, body asymmetry, micrognathia, normal head size, prominent forehead (pseudo microcephaly) and dental anomalies.
Meier-Gorlin syndrome	Microcephaly, bilateral small ears, deafness, absent or hypo-plastic patellae, cryptorchidism, hypogonadism

Cases presentation

Case 1: An 18 mouth girl was the second born child of non-consanguineous, healthy parents that she was born 40 weeks of gestation. Pregnancy was complicated by intrauterine growth retardation (IUGR). Birth weight was 1940 gr, length was 42 cm and head circumference was 31cm, that were all below the third percentile. Physical examination revealed dysmorphic feature, microcephaly, narrow face, receding mandible, pointed nose, dental altrations, microphthalmia (Figure1-a). Other findings were developmental delay in speech and motor skills, detecting strabismus and cataract in ophthalmologic tests. Her older sister had normal physical appearance and mental growth. A diagnosis of Seckel syndrome made based on these clinical findings.

Case 2: A 5 year old girl, the first born child of non-consanguineous parents who was born at preterm with gestational age of 35 weeks and IUGR delivery. Her birth weight was 870 grams, her head circumference was 25 cm and birth length of 44 cm, that were all under third percentile. Her new weight was 10 kilograms (-6.2 SDS (standard deviation score)).with head circumference of 36 cm and height of 92 cm (-3.6 SDS). In clinical findings she had severe growth retardation, microcephaly, narrow face, receding mandible, large eyes, narrow face , dental anomalies and odonthia, bilateral sensory neural hearing loss, flexion contracture of hand finger and mild mental retardation. With her clinical feature, Seckel syndrome diagnosed for her (Figure1-b).

Case 3: An 8 years old girl, the first born child of consanguineous parents (first cousin) who had IUGR at birth, (birth weight 1900 gr) and microcephaly. Growth delay continued after birth examination revealed a narrow and long mid face, high pitch voice, prominent nose, large eyes, thick eyebrows and small ears. Feeding problem happened in infancy. She had the signs of premature thelarche and pubarche at the age of 7 years and had mild mental retardation. She couldn't walk until the age of 2.5 years. Skeletal imaging showed permanent fusion of two wrist bones (Figure 1c and Figure 2a). A diagnosis of MOPD type II syndrome was making based on the clinical findings in this patient.

Case 4: An 8 year old girl was referred to our department with sever growth retardation and microcephaly. Weight was 13 kg (-5.99 SDS). Height was 92 cm (-7.2 SDS)and head circumference was 43 cm. Birth history revealed that she was born at preterm (28 weeks), second child of healthy parents (first cousin).Her birth weight was 900 gr, her length was 30 cm, and head circumference was 20 cm. pregnancy complicated with bleeding fetal decelerations and premature delivery. A clinical examination revealed diagnostic features of PD in MOPD subgroup such as: microcephaly, prominent nose and eyes, hair thinness including sclap hair and eyebrows, microdontia and missing poorly roots in some teeth. Abnormality in ophthalmologic examination, high pitched nasal voice, mild mental retardation and poor sleep patterns. She had some skeletal abnormalities such as radial deviation of 4^{th} and 5th hand fingers, abnormal development of the hip and dysplasia. She had limping that make her have a surgery that showed avascular necrosis of right femoral head in x-ray (Figure 1-e, Figure 1-f and Figure 2-b). Signs of puberty occurred early at 7 years and recently she had hematologic abnormalities in her lab tests (anemia and thrombocytosis). These findings helped us to diagnose MOPD type II based on clinical features of these patients in other reports.

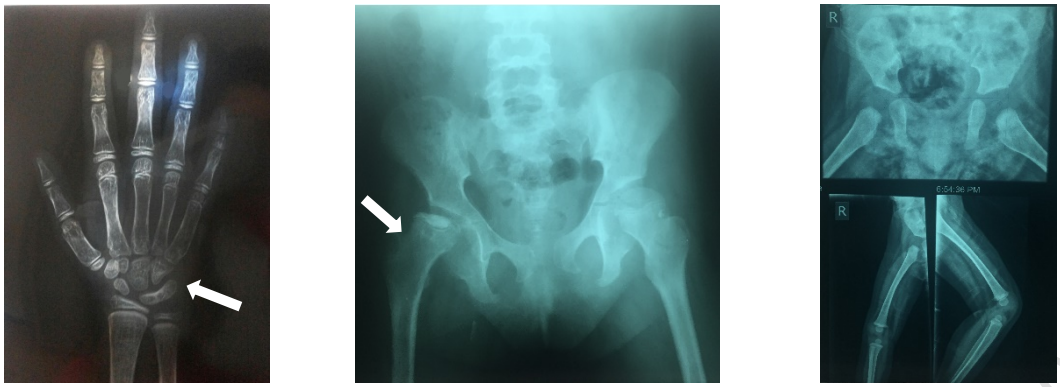
Case 5: A 12 years old girl, Second born child of consanguineous healthy parents (first cousin) that Her height was 110 cm (-5.4 SDS); her weight was 16 kg (-7 SDS) and her occipital frontal circumferences was 44 cm. she had intrauterine growth retardation (IUGR) at birth with birth weight of1680 gr, birth length of 42 cm and birth head circumference 27 cm. She exhibited microcephaly, thin hair, widely spaced primary teeth, microdontia, prominent nose and eyes, ophthalmologic disorders, delayed mental development, truncal obesity and precocious puberty (Figure 1-g and Figure 1-h).On the basis of these findings, she was diagnosed as manifesting MOPD type II.

Case 6: An 18 month boy, second born child of non-relative healthy parents, was born on IUGR at birth with birth weight 1580 gr, length 41 cm, head circumference 35 cm, growth delayed continued after birth, but head circumference was in lower limit of normal range. In our department his weight was 5500 gr (-8 SDS), his height 68 cm (-3.9 SDS), his circumference was 46 cm. Clinical findings revealed a large head compared to rest of the body (pseudomacrocephaly) , triangular small face, small jaw, thin upper lip, prominent

forehead, and, low set ear, bilateral mild hearing loss, lower limb asymmetry and diastasis in symphysis pubis in x-ray imaging (Figure 1-d and Figure 2-c), lack of appetite, developmental delay in motor skills and delayed bone age (9 months). Furthermore, he had inguinal hernia in infancy. These clinical features and normal head size can be characteristic signs of Russell silver syndrome.

Case 7: A 3.5 years old boy first born child of healthy parents, was born on 29 weeks of gestational age of pregnancy. His birth weight was 680 gr, length 33 cm and head circumference 25 cm. Growth delayed after birth except head size that was in lower normal limit. (Weight 10 kg (-4.4 SDS) and height 80 cm (-5.SDS) in 3.5 years) other clinical appearance includes triangular face, small chin, bossed forehead, low set ears and thin upper lip. He suffered from hypothyroidism and bilateral renal stones that has drug medication for treatment. These clinical appearances help us to diagnose Russell silver syndrome for him.

Figure 1. Clinical features of Primordial Dwarfism patients.
(a) and **(b**) Seckel syndrome: Note microcephaly, narrow face and forehead, low set ear, receding mandible and micrognathia;
(c), (e), (f), (g) and **(h)** MOPD type II: Note microcephaly, long mid face, prominent nose and eyes, thick eyebrows;
(d) Russell silver syndrome: Note large head (pseudo macrocephaly), triangular small face, prominent forehead, low set ears, small jaw and thin upper lip.



(a) (b) (c)

Figure 2. X-ray features of patients.
(a) Hand x-ray of Case 3: Note low bone density and fusion of two wrist bones;
(b) Pelvic x-ray of Case 4: Note avascular necrosis of right femoral head (AVN);
(c) Pelvic x-ray of Case 6: Note bone diastasis and lower limb asymmetry.

Materials and Methods

In this study we reviewed 7 cases with clinical features of growth insufficiency including prenatal and postnatal growth delay and suspicious signs of primordial dwarfism. It was a first case series of PD cases in Iran, so to compare our results with other reports , we conducted a literature review a bout primordial dwarfism on Google scholar and Medline in PubMed area. PD is a rare disorder with a spectrum of clinical conditions, so we used those articles that could help us to explain the clinical symptoms and sings of PD.

Results

In this case series we report on 7 patients with prenatal and postnatal growth retardation and diagnostic clinical features of primordial dwarfism. Our cases were small for their gestational age at birth or premature. Postnatal growth rate has progressed very slowly. Our findings to diagnosis of PD were based on severe growth retardation at birth and after then and special clinical features that helped us classified them as separate subgroups of PD. Different laboratory tests have been checked in all cases to differentiate from other disorders that may overlap with primordial dwarfism, such as Fanconi .anemia, Bloom syndrome, 3M syndrome and etc.(1). Laboratory tests were included complete blood cells, liver and renal function tests, TSH and T4, serum insulin and glucose, LH and FSH, growth hormone level, and immunologic tests. The wrist x-ray were taken for estimating bone age in all patients. Additional evaluation accomplished according of primary diagnosis in other centers ,such as abdominal Ultra sonography and brain MRI there were abnormal.

We describe these cases on the base of specific clinical appearance of PD. Today there many reports from different countries that present these cases with various presentation, some of them have genetic and molecular analysis and have confirmed it, but because of our

limitation we couldn't use genetic assay. In detail, we have 2 case of Seckel syndrome, 3 cases of MOPD type II and 2 cases of Russell Silver Syndrome. Parents accepted for present their cases in our study, we had 2 other cases that their parents didn't let us report them, so we couldn't introduce them. Summary of data these7 patients discussed in Table 2.

Table 2. Summary of data on seven cases of Primordial dwarfism

No. of case	Sex/Age	Birth weight	Head size	Facial features	Other distinguishing features	Clinical diagnosis
1	F 1.5yr	1940gr (IUGR)	microcephaly	narrow face, receding mandible, pointed nose, dental alterations, microphthalmia	Strabismus and cataract	Seckel Syndrome
2	F 5yr	870 gr Preterm (35w)	microcephaly	narrow face, receding mandible, large eyes, low set ears, dental anomalies and odontia,	bilateral sensory neural hearing loss, flexion contracture of fingers	Seckel Syndrome
3	F 8yr	1900 gr (IUGR)	microcephaly	narrow and long mid face prominent nose, large eyes, thick eyebrows and small ears	high pitch voice, Feeding problem	MOPD type II
4	F 8 yr	900 gr (28w)	microcephaly	prominent nose and eyes, hair thinness including sclap hair and eyebrows, microdontia and missing poorly roots in some teeth	avascular necrosis of right femoral head ,anemia , thrombocytopenia, radial deviation of 4th and 5th hand fingers	MOPD type II
5	F 12yr	1680gr (IUGR)	microcephaly	microcephaly, thin hair, widely spaced primary teeth, microdontia, prominent nose and eyes	delayed mental development, truncal obesity and precocious puberty	MOPD type II
6	M 1.5yr	1580 gr (IUGR)	Normal	triangular small face, small jaw, thin upper lip, prominent forehead, and, low set ear,	bilateral mild hearing loss, lower limb asymmetry and diastasis in symphysis pubis in x-ray imaging	Russell-silver syndrome

7	M 3.5yr	680 gr (29w)	25 cm Normal for gestational age	Triangular face, small chin, bossed forehead, low set ears and thin upper lip.	hypothyroidism and bilateral renal stones	Russell-silver syndrome

Discussion and a literature review

In current study we present a report of PD cases who were referred to our center with presentation of prenatal and postnatal growth delay that were not a reason of specific disease.

PD is an incurable group of disorders caused by various mechanism that presenting with growth deficiency, facial dysmorfism, brain anomalies and result in very small body size in all life (8). Growth delay continues after birth and result in short stature.

In addition, PD is a highly heterogeneous condition with different clinical feature that can be group into five major subtypes which include Seckel Syndrome, Russell-Silver Syndrome, Microcephalic Osteodysplastic Primordial Dwarfism types I/III and II Meier-Gorlin Syndrome (1).

Seckel syndrome (SS) characterized by severe microcephaly, large beaked nose, mild to moderate mental retardation and called it bird- headed dwarfism (5). Narrow face, dental anomalies (9-10), receding mandible, micrognathia, scoliosis, hip dislocation, delayed bone age, clinodactyly, low set ear, sternal abnormalities and seizure (1, 11). Dislocation of eye lens, hypo pigmented macules and Morgagni hernia are reported in rare cases (1).

MODP type I,III is a rare disorder with autosomal recessive inheritance (12) and characteristic features are growth retardation, bone dysplasia, and central nervous anomalies (13), dry skin, thinness in skull hair and eyebrows (1).

Patients with MODP type I may have microcephaly, apnea, seizure, corpus callosum agenesis, short vertebra, bent femur and hip displacement. The signs in other subtype MOPD type III are intrauterine growth retardation, clavicles and bone anomalies (1).Recent investigations have been found evidence that MOPD types I and III are variations of one form and should be grouped together despite of radiologic and physical difference they have (13).

Majewski osteodysplastic primordial dwarfism type II (MOPD) is a distinct disorder. This rare autosomal recessive condition estimated to be the most common type of PD (14).

Patients characterize by IUGR, very low birth weight (less than 1500 gr) high pitch voice (squeaky voice), prominent nose and eyes and narrow face, microdontia or missing teeth, skeletal anomalies such as delayed bone age, thin bones, coxavara, small iliac wings, flat acetabular angle, hip dislocation at birth, short first metacarpals, carpal bones fusion(6), borderline or mild mental retardation, abnormal pigmentary changes (1, 14) , feeling problem in 80% of infants and truncal obesity, that may accelerate the puberty (15).

Another important feature of MOPD type II associated with early onset cerebrovascular disease such as cerebral aneurysm and occolusive arteriopathy (moyamoya disorders (16). Hematologic abnormalities in affected patients can happen, anemia, leukocytosis and thrombocytosis have been reported (1,15). The characteristic features in Russell silver syndrome are low birth weight, short stature, body asymmetry, (17,18) and normal head size (1). Other diagnostic features are small triangular face, micrognathia, dental anomalies, prominent forehead that makes pseudo microcephalic appearance (19).Feeding difficulties such as malnutrition, gastrointestinal reflux and vomiting are frequent signs in infants and children (20).

Meier-Gorlin syndrome or ear, patellae, short stature syndrome is another type of PD that First time in 1959 Meier et al described a case with micrognathia, microtia, absent patellae and cryptorchidism (7).

The major trial in this syndrome includes bilateral small ears, aplasia or hypoplasia of patellae, short stature with normal mentality (21).Other clinical findings include microcephaly, lower limb arthrogryposis, cryptorchidism, hypogonadism, deafness, curved clavicle and deformed ribs (1,19).

In our study we report on 7 patients with severe growth deficiency from birth and after that. The diagnosis based on severe growth retardation, specific clinical findings and rule out of other similar situations. Laboratory tests checked in all cases to differentiate from those disorders that may overlap with primordial dwarfism, such as Fanconi anemia, Bloom syndrome, 3M syndrome and etc. (1,18).

In lab examination, one of the MOPD type II cases showed anemia and thrombocytosis after two years fallow up (case4), but other tests in all patients were normal. Chromosomal studies were normal in all cases.

Radiologic studies showed delayed bone age in all patients. Other findings included thin bones and avascular necrosis (AVN) of right head of femur (AVN type3) in our 4th case. AVN and hip instability may happen in underlying disorder or growth hormone therapy in PD patients. Another finding was carpal bones fusion that showed in figure 2.

Screening brain imaging for cerebrovascular disease have been done in which were normal. Cerebral vascular disease can happen in 32% of in cases of MOPD type II. Occlusive arteriopathy can be clinically silent and occurred in younger individuals (16).

Recent studies have suggested that different clinical findings showed by PD patients can be due to mutations of various genes (3).Also chromosomal studies have reported specific changes in different subtypes of PD(1).Findings of molecular, genetic and chromosomal changes can be useful experience for differentiate PD subtypes from each other. This may help for screening and prenatal diagnosis of families in future. Management of PD patients is a problem to be result in improvement of final stature. Recently, studies showed that there is no effective treatment for some parts of primordial dwarfism. Growth studies have been showed that human growth hormone (GH) therapy can improve final height and positive growth response (22).Many investigations have done to estimate the effect of GH therapy in

different types of PD .Most of these studies showed no improvement in final stature after GH therapy in MOPD type II patients. There is no study on MOPD type I/III (1).In one study birbaek et al showed improvement in growth velocity after GH therapy in seckel cases (1), but other studies haven't approved it yet. Also in Munnik et.al study an increase in growth velocity after GH therapy in Meire–Gorlin Syndrome have been reported (1).

Russell-Silver-Syndrome (RSS) is an indication for GH therapy under the SGA registered license in USA and European Medicine Agency. The results of clinical trials approved GH therapy for patients with RSS (23).

We have used GH treatment in our 2 cases of Russell silver syndrome from 4 months ago .Both of them had response to GH therapy with increase of 3-4 cm in height (length for head z score improved from -5.7 to -4.8 in case 6 and from -5 to -4.2 in case of 7), that showed benefit in our patients. All these studies showed that GH treatment can be useful for some subtypes of PD, but further studies are necessary to appoint the indications of GH therapy for primordial dwarfism patients.

Conclusion

This review and case presentation has reported with an aim to present an overview of clinical features of PD patients ,but we couldn't confirm these findings with genetic analysis .So, we hope that further studies will advanced to show molecular and chromosomal alterations for discuss overall spectrum of this disorder.

Conflict of Interest: none

Acknowledgment: none

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