Case Report

Clinical Findings and Dental Manifestations Associated With Microcephalic Osteodysplastic Primordial Dwarfism Type II: A Case Report

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ABSTRACT

Background: Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD II) is a rare untreatable genetic disorder characterized by severe prenatal and postnatal growth retardation, microcephaly, bird-headed face (receding forehead and chin, a beaklike nose, and prominent eyes), skeletal abnormalities, abnormal dentition, abnormal hair and skin changes, high-pitched nasal voice, and an increased risk for insulin resistance and cerebrovascular disease. MOPDII is caused by mutations in the pericentrin gene and is inherited in an autosomal recessive manner. This study aims to report a MOPD II child patient.

Case Presentation: A seven-year-old girl genetically diagnosed with MOPD II has been presented in this case report. Clinical, radiological, and laboratory findings with emphasis on oral features have been reported, and her dental problems management has also been described.

Conclusion: MOPD II patients have a shorter life expectancy. The main health complications which need regular care include vascular changes of the central nervous system, diabetes mellitus, renal problems, blood pressure, cardiac pathologies, and hematologic profile. MOPD II patients have a high risk of caries because they consume soft and cariogenic foods due to microdontia, oligodontia, and an incompetent masticatory system. On the other hand, dental treatment for such patients can be very challenging. MOPD II cases and their families should be aware of the importance of oral hygiene and routine dental follow-ups.

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Introduction

Primordial dwarfism (PD) is a rare group of genetic disorders characterized by prenatal and postnatal growth retardation that occurs as a result of disorganized molecular, genomic, and chromosomal changes within the embryonic stage. PD cases are diagnosed with some characteristics such as low birth weight, small bones, and body organs for gestational age (SGA), abnormal facial appearance, etc. [1]. Five major subtypes of PD including Seckel Syndrome (SS), majewski or microcephalic osteodysplastic primordial dwarfism (MOPD type I/III), MOPD type II, Meier-Gorlin syndrome, and Russell-Silver syndrome (RSS) have been delineated [1]. There is no known treatment for PD so far, unlike some non-primordial dwarfism which may be treated with growth hormones (GH) [2]. MOPD is a rare autosomal recessive group of PD characterized by severe prenatal and postnatal growth retardation and some phenotypes such as microcephaly, and bird-headed face [3].

Majewski et al. described MOPD syndrome as three distinct types (I, II, III) in 1982 [4]. Radiologic bone abnormalities, absent or mild mental retardation, and more severe growth retardation in MOPD differentiated it from Seckel syndrome [5]. MOPD II is the most common and well-described type of MPD. Additional to MPD classic features, some features of MOPD II cases include other typical characteristics such as skeletal abnormalities, abnormal dentition, abnormal hair, and skin changes, etc. which are summarized in more detail in Table 1 [1, 5, 6-9]. MOPD II is genetically homogeneous and caused by loss-of-function mutations in the pericentrin (PCNT) gene, which is present on chromosome 21q22.3 [10]. PCNT features a role in cellular division, cytokinesis, and segregation of chromosomes, and mutations of PCNT cause a decrease in total cellularity and also neuronal cellularity of the embryo [7, 8]. Kantaputra et al. have demonstrated that PCNT plays an important role in the development of the tooth, especially permanent dentition [11]. This is a report of a seven-year-old girl who was initially diagnosed with Seckel syndrome by a pediatric endocrinologist, but after a recent genetic analysis, the genetic diagnosis was MOPD II. Clinical, radiological, and laboratory findings with emphasis on oral features have been presented, and her dental problems management has also been described.

Case Presentation

History: A seven-year-old girl from Tekab city of West Azerbaijan province was referred to the Zanjan University of Medical Sciences, School of Dentistry, with chief complaints of severe pain in the left mandibular permanent first molar. Before initiation of getting history and any examination, informed consent was taken from her family, and all procedure was explained to them in detail. At the birth time, both parents were at the age 22. According to the patient's mother declarations, she had a healthy and comfortable pregnancy, and there was neither history of medication consumption except for multivitamins and iron. The childbirth was natural in the 36th gestational week. At birth, the height was 40 cm, the weight was 1450 g, and the head circumference was 28 cm. After birth, the growth velocity was very slow (2 cm per year). Her physical development was slightly retarded, but the exact time was not evident. She had difficulty with speaking and receiving speech therapy. At the age of four, she was diagnosed with Seckel syndrome based on her phenotypical features by a pediatric endocrinologist, and GH was prescribed for 12 months, but it was not effective. Recently, at the age of seven, a homozygous likely pathogenic variant in the *PCNT* gene was identified and the genetic diagnosis was MOPD II.

Clinical examination: She was proportionately short with short stature, short extremities, and a small head. Her height was 76 cm (exactly in line with the average height predicted for 7-year-old children with MOPD II), her weight was 8 kg (exactly in line with the average weight predicted for 7-year-old children with MOPD II), and her occipitofrontal circumference was 40 cm. She had a bird-like face appearance (e.g. receding forehead and chin, a beaklike nose, and prominent eyes). The nose was prominent and the columella was below the alae nasi. The ears were small but had normal morphology. She exhibited sparse and fair hair, eyelashes, and eyebrows (Figure 1). Hypopigmented macules were detected on the skin of the trunk and limbs, but no spots were found on the face (Figure 2A, B, C, and D).

The fifth digit clinodactyly in both hands was discerned (Figure 2A). A bilateral flat foot was also seen (Figure 2B). She had a high-pitched nasal voice (squeaky voice) and was not able to speak in full sentences. Intellectual development was normal. The patient was active, kind, and friendly, but her collaboration on taking radiographic images and dental services were weak.

Oral clinical, radiological, and histopathological examination: Intraoral examination along with panoramic

Table 1. Manifestations of individuals with MOPD II

Variables	Contents
Growth	Extreme growth failure from the early fetal stage onwards; premature delivery; low birth height, weight, and head circumference; lean and with decreased subcutaneous fat in the first few years of life (if not overfed); development of truncal obesity from the age of 5 or 6 years and onwards, particularly through puberty
Development	Normal intellectual development in most individuals; acute cognitive decline (a presenting sign of the moyamoya); retarded statomotoric and language development; typical progression of sexual maturation and development; precocious onset of puberty in girls over 8 years of age; normal menses in adult woman; no documented pregnancies have occurred in adult women, and no adult men are documented to have fathered children; polycystic ovaries
Skeletal	Delayed bone age Scoliosis (particularly in girls in late childhood or at puberty) Skull Large sella turcica; premature closure of cranial sutures Pelvis High, narrow pelvis; coxa vara; small iliac wings; flat acetabular angles; dislocation or subluxation of the hips Limbs Thin long bones with a progressive widening of the metaphyses and epiphyseal ossification delay; short bowed radii; short bowed ulnae; v-shaped flaring of distal femoral metaphyses; proximal femoral epiphysiolysis; short, bowed femora; short, bowed tibiae; metaphyseal flaring; dislocation, or subluxation of radial heads (subsequent decrease range of motion in the elbow); the patellae are present and appear to be of proportionate size; more prominent knees that can dislocate laterally because of loose lateral ligaments; mesomelia Chest Narrow chest; long, slender, straight clavicles; hypoplastic scapulae Hands Brachydactyly; short distal phalanges; metacarpal pseudoepiphyses; fifth finger clinodactyly; the fusion of the phalanges; short first metacarpals; brachymesophalangy; ivory and cone-shaped epiphyses (disappears with age); angular scaphoid and trapezium bones Feet Bilateral flat foot; distal symphalangism; long second toe
Craniofacial	Microcephaly; characteristic bird-headed face (micrognathia receding forehead, prominent eyes, beaklike nose); prominent nose with a wide bridge and broad root; the nasal tip is full and the columella often lies below the alae nasi; ears are normal or mildly dysplastic with attached lobules and typically normal position; down slanting to the palpebral fissure; large sella turcica; premature closure of cranial sutures
Dental	Hypodontia; oligodontia; microdontia; abnormal tooth morphology; enamel, dentin, and cementum hypoplasia; Opalescent teeth; spacing; absent or short roots; single root molars; malformation of mandibular premolars; delayed dental development of deciduous teeth; premature exfoliation of deciduous teeth; accelerated eruption of permanent dentition; hypoplastic maxillary and mandibular arches
Cardiac	bicuspid aortic valve defect; atrial septal defect; patent ductus arteriosus; narrowing of the left anterior descending coronary artery (LAD) and a narrowing of the first diagonal branch has been seen; myocarditis; myocardial infarct
Neurologic	Absent or mild mental retardation; developmental delay (mild-severe); structural or myelinization abnormalities of the CNS; abnormal gyral patterns; cysts of the corpus callosum and sella areas; hypoplasia of the corpus callosum; multiple aneurysms; moyamoya disease; infarct
Renal	Infrequent structural abnormalities, as well as nephrolithiasis; two individuals have undergone a renal transplant for chronic renal failure of uncertain etiology; hypertension
Endocrine	Type II diabetes (insulin resistance is common, it is not congenital but most commonly acquired between 5-10 years of age); premature puberty; the normal range of growth hormone
Hematologic	Asymptomatic thrombocytosis; leukocytosis; anemia; mild iron-deficient anemia can develop in post-menarche
Dermatologic	Areas of hypopigmentation and hyperpigmentation; café au lait spots; cutis marmorata and mottling (especially in infancy); development of multiple creases on the hands and feet with aging; increased dark pigmentation around the neck, trunk, and in the axilla in school-aged children (given the subsequent recognition of insulin resistance in this population, and the fact that these areas do darken with sun exposure or growth hormone treatment, true acanthosis nigricans is probable); development of areas of hypopigmentation and dry skin later in life; sparse scalp hair; hair thinning of scalp hair, eyelashes, and eyebrows; thick eyebrows
Ophthalmologic	Esotropia; farsightedness; astigmatism

Table 2. Differentiating features of subtypes of primordial dwarfism

Subtypes	Inheritance Pattern	Gene Involved	Head Size	Distinguishing Clinical Findings
Silver-Russell syndrome	Autosomal dominant or autosomal recessive and genomic imprinting	*CUL7, OBSL1, SGCE, ZFP57, NF1, CSH1*	Normal	Small triangular face, micrognathia, dental anomalies, feeding difficulties
Meier-Gorlin syndrome	Autosomal recessive	*ORC1, ORC4, ORC6, CDT1, CDC6*	Microcephalic	Small ears, absent/hypoplastic patellae
Seckel syndrome	Autosomal recessive	*ATR, ATRIP, CENPJ, CEP152, CEP63, RBBP8, NIN, DNA2*	Microcephalic	Extremely small head with a narrow face, dental alterations, beak-like protrusion of nose, receding mandible and forehead
MOPD type II	Autosomal recessive	*PCNT, IGF1R*	Microcephalic	Prominent nose and eyes, abnormally small or missing teeth, a high squeaky voice, absent or mild mental retardation
MOPD type I/III	Autosomal recessive	*RNU4ATAC*	Microcephalic	Dry skin, sparsity of hair, eyelashes, and eyebrows

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image (Figure 3A, B, and C) showed the following findings: Hypoplastic alveolar process, poor periodontal support of teeth, generalized spacing, microdontia, oligodontia, enamel hypoplasia, the layered look of the enamel, abnormal morphology of teeth, short and conical roots, taurodont like the appearance of the molars, the club-shaped appearance of the roots of the mandibular incisors, generalized grade II mobility, the presence of teeth numbers 16, 53, 11, 51 (or 61), 21, 62, 63, 26, 36, 73, 72, 32,31,41,42, 43, 46, the presence of permanent teeth buds in teeth numbers of 17, 15,14, 13, 23, 24, 25,27, 37, 34, 33, 44, 47, and deep caries in teeth numbers of 16, 53, 62, 63, 26, 36, 73, 72, 46 (teeth numbers are based on World Dental Federation (FDI)). Although the lateral cephalometric radiograph (Figure 3D) was not flawless due to the low cooperation of the child, it revealed a large sella turcica, skeletal class II (mandibular deficiency), increased mandibular plane angle, skeletal open bite, dental deep bite, vertical growth pattern, and retroclined incisors. After extraction of the hopeless teeth and decalcification, the histopathologic evaluation revealed atypical dentin structures containing fewer and irregular dentinal tubules within atypical interglobular calcification. Hypocalcified and hypoplastic cementum were seen in some areas of roots. The pulp chamber was also small-sized, containing calcified particles and a few collagen fibers (Figures 4 and 5).

Laboratory findings: The results of the latest tests which were related to the age of five showed the following: All hematology complete blood count elements were within normal limits except increased platelet count, decreased mean platelet volume, increased lymphocytes count, and decreased neutrophils. In the endocrine analysis, thyroid hormones, and thyroid stimulating hormones were in the normal range, but there was an increase in insulin-like growth factor-1 (IGF-I). Biochemistry analysis of blood showed a slight decrease in creatinine, a slight increase in O_2 saturation, and a slight decrease in PCO_2. Urine analysis elements were normal.

Genetic findings: According to the genetic tests analysis and genetic counseling, the genetic diagnosis of MOPD II was confirmed and no copy number variants were detected in the analyzed genes (Figure 6). A homozygous likely pathogenic variant in the *PCNT* gene was identified. Pathogenic variants in the *PCNT* gene are associated with autosomal recessive MOPD II.

Discussion

PD is a rare and often deadly group of genetic disorders characterized by prenatal and postnatal growth retardation and other abnormalities. Manifestations of this condition first appear in the fetal stage and continue through life [1]. Distinguishing features of PD subtypes are presented in Table 2 [1, 7, 12, 13]. Genetic analysis is important for definitive diagnosis because many phenotypic features of MOPD II and Seckel syndrome overlap as seen in the present case. At least 30 mutations in the *PCNT* gene have been proven to cause MOPD II. These mutations can lead to the production of an abnormal pericentrin protein which is not able to anchor other proteins to the centrosome. Subsequently, centrosomes cannot properly assemble microtubules, and disruption of the cell cycle and cell division occurs. The final result is cell death. This extensively diminished number of cells explains signs of MOPD II such as microcephaly

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Figure 1. Proportionately short stature; bird-like face appearance; sparse, and fair hair, eyelashes, and eyebrowsSit abore nonsequos

and dwarfism [10]. The pattern of inheritance of MOPD II is autosomal recessive since consanguineous parents have been reported, but in some case reports, non-consanguineous have also been observed [9]. In the present case, the parents are fourth-degree relatives. The mother reported only consumption of multivitamins and iron although no common teratogens have been reported in the literature. Severe intrauterine growth retardation can be revealed from the ultrasound at the earliest stages of pregnancy (sonographic recognition

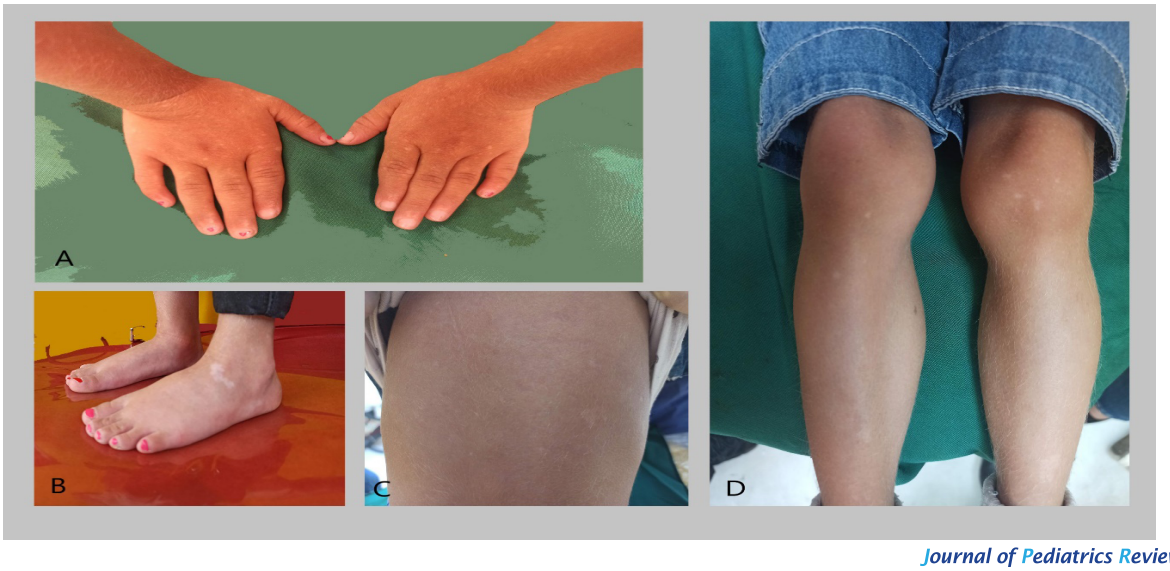

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Figure 2. A) Fifth digit clinodactyly, B) Bilateral flat foot, D) Prominent Knees, A, B, C, and D) Hypopigmented macules

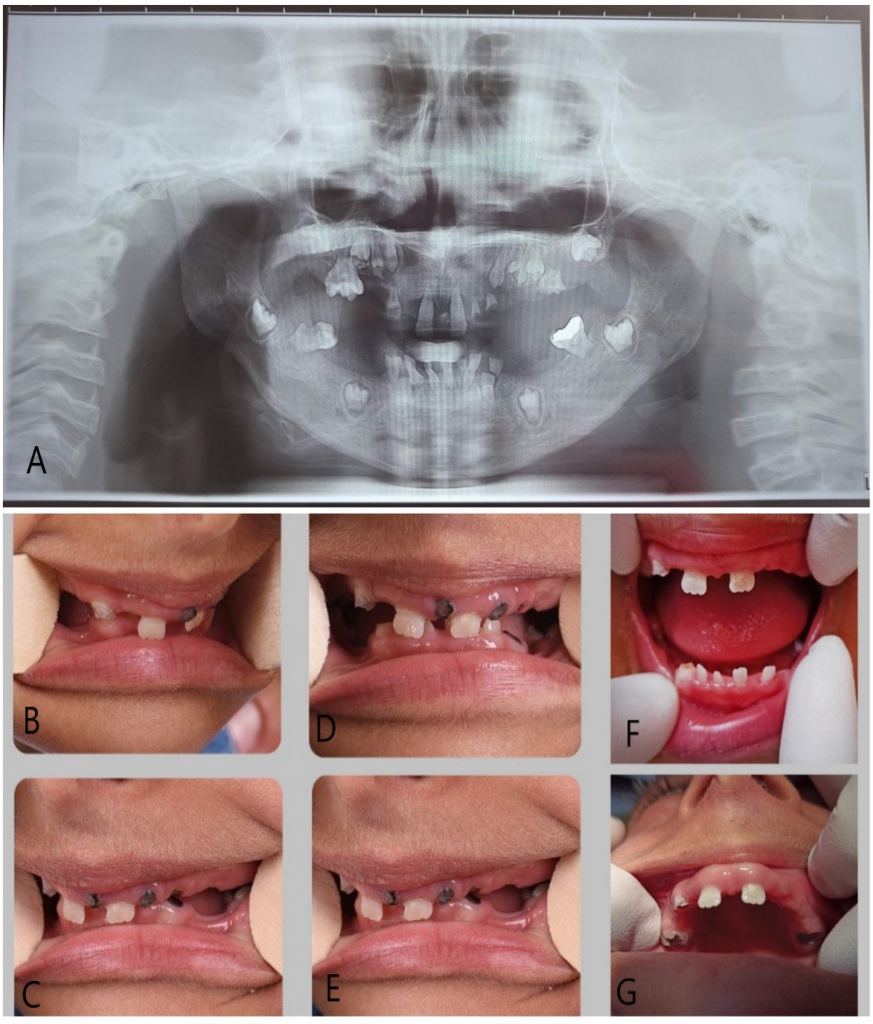

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Figure 3. A) Panoramic view radiograph, B-E) Before, F, G) after dental treatment intraoral photographs showing microstomia, oligodontia, microdontia, and teeth with abnormal crowns and roots

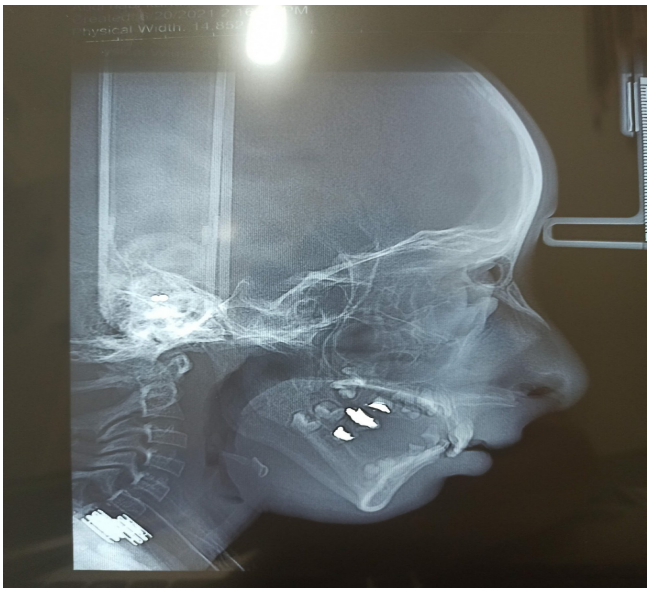

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Figure 4. Lateral cephalometric radiograph showing a large sella turcica, skeletal Cl II, and steep mandibular plane

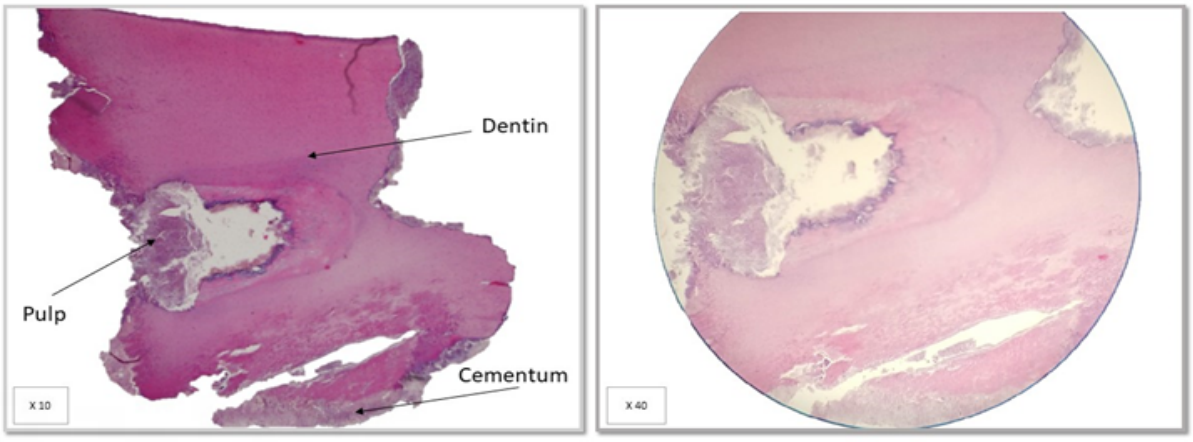

Figure 5. Histopathological image showing atypical dentin, hypocalcified and hypoplastic cementum, and small-sized pulp chamber containing calcified particles and few collagen fibers (H & E stain)

occurs between 12-14 weeks of the pregnancy), and the growth deficiency becomes progressively more severe over time during pregnancy [6]. In the present case, the ultrasonic examination was performed three times during pregnancy and it was noted that the child was small, but unfortunately, no further examination was taken.

The patient's mother gave a history of frequent hospitalization due to diarrhea and vomiting in the infancy period. It could be a result of an abnormal immune response or an increased susceptibility to infection.

For 12 months, this child has been under GH therapy. According to the evidence, GH therapy does not appear advantageous and can even have some morbidities. It is reported that individuals who received the GH may develop hyperpigmentation areas and cafe' au lait macules earlier than other individuals with MOPD II. There was some concern that GH therapy can contribute to the development of insulin resistance [6, 7]. On echocardiographic examination, the heart was unremarkable. The heart is often normal at birth, although some defects have been reported. Cardiovascular disease can develop with age throughout life and die from myocarditis and myocardial infarction can occur [6]. Because PCNT mutations are related to severe insulin resistance and type II diabetes, individuals with MOPD II should regularly test for fasting blood sugar, lipid panel, and hepatic function [14]. In this patient, blood sugar and lipid profile were within normal limits. Studies showed that low or high levels of IGF-I are associated with impaired glucose tolerance and a higher risk of type 2 diabetes [15]. In this patient, the IGF-I level was lower than the normal range at one year old, but it was higher than the normal range at three years old.

Central nervous system (CNS) vascular anomalies such as aneurysms and moyamoya disease can even develop in the early years of life. However, several individuals do not present these problems even in the second or third decades of life. These vascular changes can lead to rupture, hemorrhage, infarction, and even death. Routine screening for CNS vascular anomalies should be performed using magnetic resonance imaging (MRI) of the brain with magnetic resonance angiography of the cerebral vessels. Unlike Moyamoya, which is more frequent in children, the aneurysm is more common in older ages. Cognitive decline and mental deterioration can be a sign of the development of angiopathy [16]. No MRI of the child's brain had been performed so far. Parents were informed about this concern and referred to a specialist for regular follow-ups.

One of the most important manifestations of MOPD II patients is characteristic skeletal dysplasia, as described in Table 1. In the present report, due to the lack of cooperation of the child and parents, skeletal radiographs were not obtained, but some features like thin long bones, fifth finger clinodactyly of both hands, and bilateral flat foot were detectable in clinical examination. *PCNT* gene plays an important role in dental development. This role is more prominent in permanent dentition. Because of PCNT mutations, individuals with MOPD II show interesting dental features [13]. In this child, as seen in previous reports, the mouth was extremely small; maxillary and mandibular arches were hypoplastic; tooth buds of the mandibular second premolars were absent; teeth were small, hypoplastic, mal-shaped, short-rooted, and slightly mobile. The patient's first primary tooth was mandibu-

CLINICAL INFORMATION

The proband is a 7-year-old girl with skeletal and mental problems who received several growth injections but had no effect.

Previously the proband's maternal uncle's wife (PGERC1060, FayeghCheraghTapeh, Fouzieh) was received whole exome sequencing at PardisGene. She had a history of two therapeutically aborted sons suspicious of Meckel Gruber syndrome and two deceased children with no mentioned reason. Three heterozygous variants as carrier findings in the MKS1 (NM_017777.4:c.515+1G>A), OTC (NM_000531.6:c.76C>T) and POLG (NM_001126131.2:c.1760C>T) genes in the proband were detected. Her partner (FayeghCheraghTapeh, Rasoul) was also heterozygous for the variants in the MKS1 gene. The detected variant in the OTC gene was also detected heterozygous in the proband's mother (Kordi, Hamideh) but not in her brother (FayeghCheraghTapeh, Keyvan).

None of the detected variants in the PGERC1060 sample in the MKS1, OTC and POLG genes was detected in the patient (PGERA1179, Abdi, Sana). The detected variants in the MKS1and OTC genes were not also found in her father (Abdi, Shahab).
Genes related to the following HPO terms were applied in the analysis:
Microcephaly, Proportionate short stature, Small face, Micrognathia, Intellectual disability, Poor speech, Finger clinodactyly, Microtia, Severe failure to thrive, Abnormality of dental enamel, Dental decay, Delayed tooth eruption
Consanguinity: Yes

POSITIVE RESULT
Likely pathogenic variant was identified

- Sanger sequencing to confirm the **likely pathogenic variant in the PCNT gene as the main cause of the disease** in the proband is recommended.
- Parental carrier testing is also suggested to confirm the homozygosity of this variant.
- Genetic counseling is also recommended.

RESULT SUMMARY

Gene	Variant Coordinates	Zygosity	In Silico Parameters	Allele Frequencies*	Type and Classification**
PCNT	Chr21(hg38):g46366786 NM_006031.6:c.2812C>T p.(Gln938Ter) Exon 15/47	Hom	MutationTaster: Disease causing FATHMM_MKL: Neutral SIFT: NA	gnomAD: NA ExAC: NA Iranome: NA	Stop gain Likely pathogenic (Class 2)

*Genome Aggregation Database (gnomAD) Genome version:3.0, Exome Aggregation Consortium (ExAC) version:1.0 and Iranome **Variant classification is based on ACMG recommendations: Class 1: Pathogenic, Class 2: Likely pathogenic, Class 3: Variant of uncertain significance (VUS), Class 4: Likely benign, Class 5: Benign

VARIANT INTERPRETATION

PCNT, c.2812C>T p.(Gln938Ter)

The PCNT variant c.2812C>T p.(Gln938Ter) causes a premature stop codon at position 938. This variant is classified **likely pathogenic** according to **ACMG**. It was also reported **disease causing** by **HGMD** (PMID: 29620724).

Pathogenic variants in the PCNT gene are associated with autosomal recessive **Microcephalic osteodysplastic primordial dwarfism, type II** (OMIM: 210720).
Microcephalic osteodysplastic primordial dwarfism type II is characterized by intrauterine growth retardation, severe proportionate short stature, and microcephaly. It is distinct from Seckel syndrome by more severe growth retardation, radiologic abnormalities, and absent or mild mental retardation (PMID: 19643772).

Lin *et al.*, (1995) reported 2 African American brothers who had **microcephaly, short stature**, and generalized **microdontia** (PMID: 8533804).
Majewski and Goecke (1998) reported 3 new cases of MOPD II and reviewed 14 published cases. All children had marked intrauterine and **postnatal growth failure**, disproportionate **microcephaly**, and **mental retardation**. They were **disproportionately short statured** due to short limbs. Characteristic **skeletal anomalies** included small iliac wings with flat acetabular angles, coxa vara, V-shaped distal femoral metaphyses, and triangular distal femoral epiphyses, as well as metacarpal pseudoepiphyses, short first metacarpals, and brachymesophalangy V (PMID: 9800908).

Piane *et al.*, (2009) reported a 3-year-old Italian boy who had prenatal onset of **proportionate dwarfism, postnatal severe microcephaly**, high forehead with receding hairline, sparse scalp hair, beaked nose, **mild retrognathia,** and hypotonia (PMID: 19839044).

Weiss *et al.*, (2020) reported 2 unrelated males with MOPD II. Patient 1 had **severe prenatal microcephaly and growth delay.** At birth he had symmetric **small size and dysmorphic features** including a prominent nose, long columella, and **small jaw.** At age 14 months, he had developmental motor delay and small size. Brain MRI at age 2 years showed delayed myelination and widening of the sphenooccipital suture. At age 32 months, he had a right frontal stroke and left hemiparesis, and angiography showed 3 small middle cerebral aneurysms. At age 40 months, he had skin hypopigmentation and **malformed teeth.** A developmental assessment identified **speech and fine motor delays** (PMID: 30922925).

INCIDENTAL FINIDNGS

We did not detect any pathogenic or likely pathogenic variants in the genes for which incidental findings are reported based on ACMG guidelines.

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Figure 6. The results of genetic testing

lar central incisors and had erupted at eight months, which is almost at the normal eruption time. According to the patient's parents, all deciduous teeth were present in the child's mouth and the primary molars have been extracted due to caries. Accelerated eruption of permanent mandibular canines was seen in this present case. Among the documented case reports, the premature eruption of permanent teeth has been reported only in one case by Ghosh et al. [8].

In this patient, unrestorable teeth were extracted, teeth numbers 16 and 36 were restored using amalgam, and teeth numbers 26 and 46 were restored using amalgam after pulpotomy using MTA. Amalgam filling of tooth number 26 failed the next day, possibly due to the bowl shape and insufficient structure of the tooth; therefore, we decided to fill the cavity using resin composite. Fortunately, the new restoration was successful in the three months later follow-up. The dental treatment of patients with MOPD II might be complicated because of microstomia, microdontia, and malformed roots and crowns. MOPD II is a rare untreatable genetical disorder characterized by severe prenatal and postnatal manifestations. Clinical manifestations and radiographic features along with genetic tests help make a diagnosis. MOPD II patients have a shorter life expectancy than normal individuals, with a maximum reported age of 39 years. The main health complications which need regular care include vascular changes of CNS, diabetes mellitus, renal problems, blood pressure, cardiac pathologies, and hematologic profile. Dental problems are one of the other areas of concern. MOPD II patients have a high risk of caries because they consume soft and cariogenic foods due to microdontia, oligodontia, and incompetent masticatory systems. On the other hand, due to the small size of the mouth and the special condition of the dentition, dental treatment for such patients can be very challenging and complex. MOPD II cases and their families should be aware of the importance of oral hygiene and routine dental follow-ups.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured

about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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