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CASE REPORT

HAVING MULTIPLE RENAL CYSTS IN A YOUNG ADULT IS NOT ALWAYS A SIGN OF POLYCYSTIC KIDNEY DISEASE

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ABSTRACT

Multiple renal cysts in adult patients could have asymptomatic, benign and a nonprogressive course. However, these cysts could be renal features of a very rare hereditary, progressive syndrome defined as cranioectodermal dysplasia (CED or Sensenbrenner syndrome). Affected patients show dysmorphic features such as craniosynostosis, nail dystrophy, cutaneous dyshydrosis, dry or scaly palmar skin, trichodysplasia, deafness, pectus excavatum, telecanthus, hypertelorism, low set ears, everted lower lip, anteverted nares, short neck and height, joint laxity, inguinal hernia, widely spaced teeth, microdontia, hypodontia in addition to nephronophthisis. We report a 22-year-old male hypertensive patient with multiple renal cysts and dental malformations listed as malocclusion, screwdriver shaped crowns, widely spaced front teeth, microdontia and hyperdontia. Molecular analysis reported missense p.(Ala875Thr) and p.(Lys969Asn) variants in the *WDR35* gene. The 1-year follow-up of this case provided the knowledge that angiotensin II receptor blocker drug (olmesartan) reduced the microalbuminuria to normal levels and preserved the renal functions. We suggest interdisciplinary studies, especially intraoral and genetic evaluations for patients with cystic renal diseases. For the first time we report that hyperdontia could be found as a dental feature of CED.

Keywords: Ciliopathies; Cranioectodermal dysplasia (CED); Cystic; Kidney diseases; Syndrome.

INTRODUCTION

Cystic kidney diseases are commonly discovered by renal imaging methods in adult patients. Simple renal cysts are the most common (65.0-70.0%) types of all the renal masses [1]. The incidence of simple renal cysts increase by aging with an incidence of zero between 15-29 years of life. Thus, it is especially necessary for young patients to differentiate the simple cysts from more serious types such as polycystic kidney disease (PKD), renal abscess, cystic carcinoma and nephronophthisis. Among these ciliopathies, a very rarely reported syndrome is cranioectodermal dysplasia (CED), which should be considered for young adults, as one of the clinical features of CED is nephronophthisis [2]. Here, we report a 22-year-old male patient with multiple bilateral renal cysts finally diagnosed as CED (or Sensenbrenner syndrome) by genetic testing.

CASE REPORT

A 21-year-old male patient presented at the Department of Nephrology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey, with a family history of renal failure; his younger brother and cousin came to the hospital 1 year ago. Consanguinity between his parents was not present. He was asymptomatic. His height was 165 cm, and weight was 53 kg. His blood pressure was 140/100 mmHg. Eye examination revealed grade 2 hypertensive retinopathy (retinitis pigmentosa was not observed). The irregularly shaped right kidney was palpated. There was

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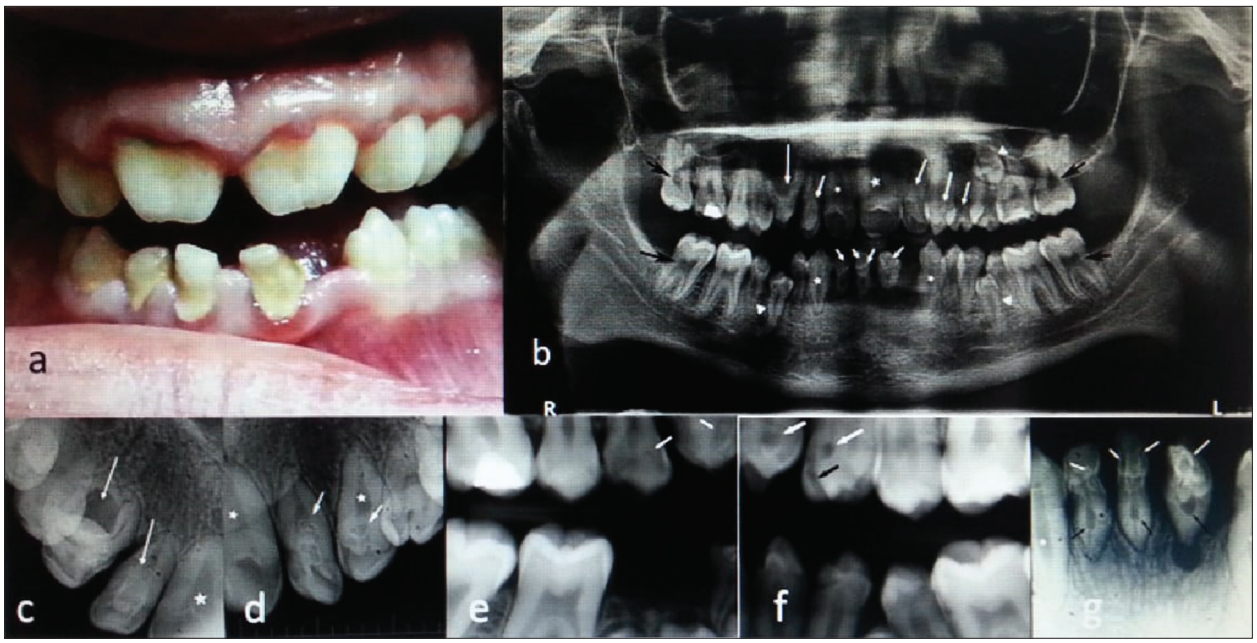

Figure 1. Intraoral features of the patient are: **(a)** malocclusion, screwdriver shape crowns (teeth 11, 21) (note that upper central teeth do not have central lobe), mandibular anterior diastema, microdontia (teeth 31, 41, 42) (the teeth were numbered by the FDI system), calculus formation, periodontitis, and tooth exfoliation (tooth 32) in the mandibular anterior region. **(b)** Multiple dens invaginatus (DI) (white arrows), large pulp chambers (white stars), impacted supernumerary teeth in bilateral mandibular and left maxillary premolar regions (white arrow heads), one erupted supernumerary toot left lower premolar region and hypotaurodontism in the all second molar teeth (black arrows) seen in panaromic image. In periapical and bite-wing images: **(c)** large pulp chamber in the right upper central (white star), type 2 DI in the right upper lateral, type 3 DI in the right upper canine (white arrows); **(d)** large pulp chambers in the left upper central and canine (white stars), type 2 DI in the left upper lateral and type 1 DI in the left upper canine (white arrows); **(e)** DI in the right upper canine and type 1 DI first premolar (white arrows); **(f)** type 1 DI in the left upper canine and first premolar (white arrows) and a groove on the buccal surface of tooth 24 crown (black arrow); **(g)** Type 2 DI in the left lower central, type 1 DI right lower central and lateral (white arrows), pulp anomaly (thistle tube appearance) in the mandibular incisors (black arrows) and large pulp chambers in lower canines (white stars) were seen.

no sparse or absent hair, unusual facial shape (frontal bossing), nail dystrophy, cutaneous dyshydrosis, dry or scaly palmar skin, trichodysplasia, deafness, pectus excavatum, telecanthus, hypertelorism, low-set ears, everted lower lip, anteverted nares, short neck and height, joint laxity, inguinal hernia. Malocclusion, screwdriver-shaped crowns [teeth 11 and 21; the teeth were numbered by the Fédération Dentaire Internationale (FDI) system], widely spaced front teeth (anterior mandibular diastema), microdontia (teeth 31, 41 and 42), calculus formation, loss of attachment and severe teeth mobility in the mandibular anterior region, early tooth exfoliation (tooth 32) (Figure 1a), groove on the buccal surface of tooth 24, fordyce granules on lips edges were found on extraoral and intraoral examination (Figure 2b). Results of biochemical tests were as follows: serum creatinine level: 1.26 mg/dL, uric acid: 7.8 g/dL, albumin level: 4.7 g/dL, phosphorus: 2.37 mg/ dL, urinary albumin excretion: 49.0 mg/day, proteinuria: 104.0 mg/day, creatinine clearance (from a 24-hour urine collection): 51 mL/min., and estimated glomerular filtration rate (eGFR) Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI Creatinine Equation): 80.0 mL/min./1.73 m^2.

Ultrasonographic examination revealed normal sized kidneys with bilateral multiple cysts (6-7 cysts in each kidney) and computed tomography (CT) imaging confirmed the cystic kidney disease (Figure 3a). Radiographical examination showed mandibular retrognathia (Figure 2a), hyperdontia in bilateral mandibular and left maxillary premolar regions, severe resorption of alveolar bone in the anterior mandibular region, and root and pulp anomaly (thistle tube appearance) of teeth 31, 41 and 42, multiple dens invaginatus in the jaws (Figure 1b-g), positive metacarpal sign indicating small dimensions of the fourth metacarpal and thick distal phalanx of the thumb (Figure 2d). Ambulatory blood pressure monitoring revealed hypertension [average 24-hour blood pressure 125/87 mmHg (≥130/≥80 mmHg)] [3]. Perindopril was prescribed for arterial hypertension, however, due to side effects (diarrhea and chest pain) perindopril was switched to olmesartan (10 mg/day). Genetic analysis was planned in order to find a definitive diagnosis.

Genetic analysis of the patient revealed a heterozygous (monoallelic) mutation of c.2623G>A p.(Ala875Thr) and c.2907G>T p.(Lys969Asn) on the *WDR35* gene (OMIM #613610). Based on this genetic test, dental dys-

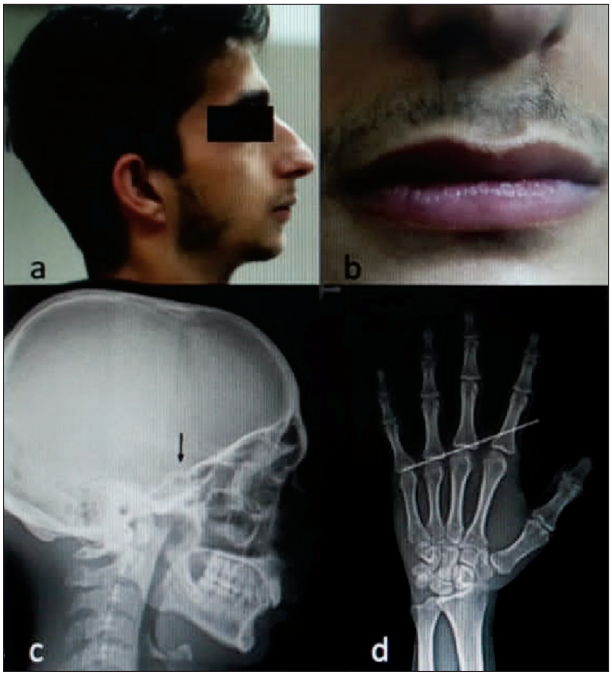

Figure 2. Extraoral features of the patient are: **(a)** retrognathia inferior and nasal hump; **(b)** Fordyce granules on lips edges; **(c)** Sella Turcica bridge was observed in the lateral cephalometric image (black arrow); **(d)** hand-wrist radiographic image showing slightly small dimension of fourth metacarpal (positive metacarpal sign) (white line). In addition, thick distal phalanx of thumb was revealed.

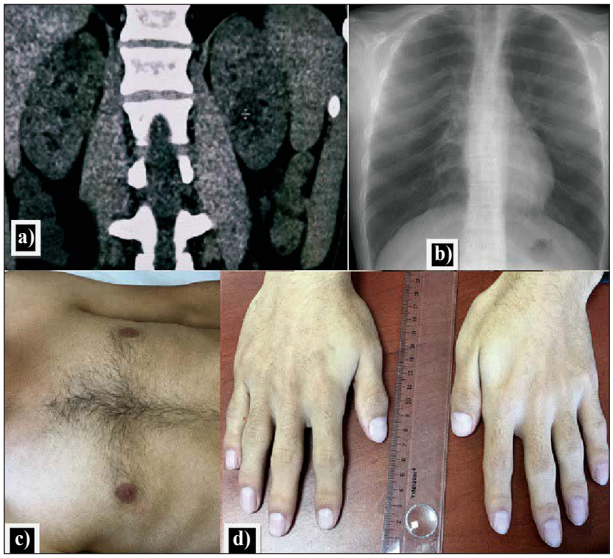

Figure 3. (a) Computed tomography coronal section that displays bilateral multiple renal cysts; **(b)** chest X-ray showing normal ribs and lungs; **(c)** normal respiratory examination with inspection; **(d)** no obvious nail and finger deformity was found on inspection of the hands.

plasia and renal cystic malformations were diagnosed as phenotypic features of CED type 2 [4]. The patient has been treated with olmesartan for 1 year, and he is well with a blood pressure of 110/70 mmHg, albuminuria of 11.0 mg/day and creatinine clearance of 81.0 mL/min. Written informed consent for publication of this case report was obtained from the patient.

DISCUSSION

Cystic renal diseases are classified into three groups on the basis of clinical, pathological and genetic features as hereditary, dysplastic (multicystic, obstructive cystic) and non hereditary non dysplastic (cystic tumors, simple renal cysts). Hereditary cystic renal diseases are caused by primary ciliopathies. Primary ciliopathies are a group of diseases secondary to genetic disorders leading to defective ciliary formation and/or functions. Autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), and cysts with syndromes (glomerulocystic and medullary cystic dysplasia, nephronophthisis) are hereditary cystic renal diseases that may share similar clinical features and genetic overlap affecting mostly kidneys, eyes, bones, brain and liver [5,6]. Among these hereditary cystic diseases, cysts with syndromes are usually not investigated as they are very rare.

Polycystic kidneys (a total of ≥three cysts) at a young age (15 to 29) with presence of renal disease in a younger brother and first degree cousin, as in our case, usually make clinicians diagnose the etiology as ADPKD or ARPKD [7,8]. However, these patients should be evaluated for cysts with syndromes such as CED, as in our case. To date, nearly 70 cases diagnosed with CED have been reported [9]. Although the mode of inheritance of this syndrome is autosomal recessive, consanguinity was not present in our patient's family history.

The phenotypic expressions of CED are heterogenous due to pleiotropic effects of mutations. For example, some of the frequent (>75.0%) and common (50.0-70.0%) features of CED such as narrow thorax, characteristic facial features (low-set ears, everted lower lip, frontal bossing), brachydactyly, dysplastic ribs, sparse hair, dry and scaly palmar skin, dolichocephaly, joint laxity, liver disease, abnormal nails and syndactyly, were not present (Figure 2a, 3b, 3c, 3d), while the other common features such as nephronophthisis and dental malformations, were present in our patient, whose diagnosis was confirmed molecularly [10]. The other less common (25.0-50.0%) features (developmental delay, heart defect, recurrent lung infections, bilateral umbilical hernia and polydactyly) and infrequent (<25.0%) features (hip dysplasia, cystic hygroma and retinal dystrophy) were not found. Our patient had some other features (foreshortening of the fourth metacarpal with posi-

tive metacarpal sign, thick distal phalanx of the thumb), which were not reported previously in patients with CED.

Normal-sized or small-sized kidneys with cysts and increased echogenicity, tubulointerstitial nephritis, hypertension, nocturia, hematuria, proteinuria and development of end-stage kidney disease ,are usually found as renal involvement in patients with this syndrome [10]. Our patient had hypertension, normal-sized kidneys with multiple cysts, and a mild degree of renal insufficiency. Characteristic dental features of this syndrome involve hypodontia, microdontia, taurodontism, fused decidious teeth, widely-spaced hypoplastic teeth [2,10,11]. Dental abnormalities of our case were malocclusion, screwdriver-shaped crowns, widely spaced front teeth, microdontia noticed in the mandible, loss of attachment and severe tooth mobility in the mandibular anterior region, mandibular inferior retrognathia, thistle tube appearance and hyperdontia. Hypo-taurodontism was observed in all second molars according to Shifman and Chanannel [12]. Since the patient was 21 years old, the findings of deciduous teeth could not be evaluated. Unexpectedly, hyperdontia was noticed in three quadrants. In addition, nail and hair structures were also normal. Considering thistle tube appearance, it is one of the radiographic features of the hereditary dentin dysplasia (DD) type II that is categorized among dental anomalies with autosomal dominant pattern of inheritance [13]. Our patient had this special shape of the pulp chamber regarded as a thistle tube appearance in the lower anterior teeth. However, other features compatible with DD type II such as obliterated pulp chambers, thread-like root canals, multiple pulp calcifications, were not found in the present case. Screwdriver-shaped teeth were reported in patients with Nance-Horan syndrome, Cockayne syndrome, Kallmann syndrome, Williams syndrome and Kabuki syndrome [14-18]. Existence of renal cysts, lack of mental retardation, cataract, strabismus, cerebral leukodystrophy, deafness, and other systemic features, was also considered as basic features in differential diagnosis besides molecular analysis. Genetic examination has confirmed the diagnosis of CED. We suggest clinical and multidisciplinary approach for differential diagnosis of these patients. This case is the first article reporting hyperdontia (a total of 31 teeth and absence of third molars) as the clinical feature of CED.

Learning Points. Herein, we have described a patient who was diagnosed with CED in his third decade of life. Intraoral examinations, search for nail and finger dysplasia are necessary in differential diagnosis of renal cystic diseases. The definitive diagnosis should depend on genetic testing with suspicion due to clinical signs. Based on the present case, we intend to emphasize the approach, especially for young patients with multiple renal cysts, in order to diagnose ciliopathies precisely.

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Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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