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CLINICAL STUDY

Overview of typical dental abnormalities in rare genetic syndromes occurring in the Czech Roma population

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ABSTRACT

BACKGROUND: The Roma population is a genetically isolated population with a shared origin, totaling between 10 to 14 million individuals worldwide, stemming from a limited number of "genetic founders". Roma individuals exhibit specific hereditary diseases, often stemming from recessive genetic variants due to a higher degree of consanguinity, with recent molecular-genetic investigations shedding light on several conditions prevalent within the Czech Roma population. However, an overview of stomatological issues in diagnosing such diseases proves challenging, leading to frequent underdiagnosis or misdiagnosis.

METHODS: The contribution monitors the clinical description, typical symptoms and treatment options including dental abnormalities in rare genetic diseases in the Roma population which are treated in ERN CRANIO centre at Motol University Hospital in Prague.

RESULTS: Our research provides examples of autosomal recessive diseases, which can be molecularly confirmed, and prevalent within the Roma community. These include congenital cataract syndrome, facial dysmorphism and demyelinating neuropathy, non-syndromic prelingual e.g. deafness with *GJB2* gene impairment, and myasthenic syndrome.

CONCLUSION: Our report aimed to provide a systematic review of dental phenotypes which can relate to Czech Roma's rare genetic disorders therapy including dental treatment. Understanding is important for preventing unterdiagnosis or treatment for the patients affected review of observed *(Fig. 6, Ref. 27)*. Text in PDF www.elis.sk

KEYWORDS: Roma, rare and facilitate treatment, dental anomalies, congenital cataracts, pathogenic variants.

Introduction

The European Roma community traces its roots to the Indian Dalit caste, the lowest tier of India's caste system, migrating from the Indian subcontinent around a millennium ago. Documentation of their journey to Europe dates to the 3rd–10th centuries (1), with initial settlements in Byzantium, followed by movements through Iran, the Caucasus, and modern-day Romania in the 11th century. By the 12th century, they had dispersed across Europe.

Genetic studies indicate the common origin of European Roma from a single founding population in northwestern India approximately 1500 years ago (2, 3). The term "Gypsy" derives from the Greek word *Atsinganoi*, used to identify this ethnic group in the Byzantine Empire. Legends suggest they undertook a pilgrimage to Egypt as penance for abandoning Christianity. The Roma population's high level of homozygosity suggests long-term genetic isolation (2). Today, they are the most populous minority group in Europe, numbering between 10–12 million individuals (4), with significant percentages in Bulgaria (10%), Slovakia (9%), and Romania (8%). In Western Europe, Spain hosts the largest Roma Central and Eastern Europe (2). However, the Roma community faces socio-economic challenges, reflecting poorer health outcomes (3). In Spain, they have higher infant mortality (4), poorer health status (5), and a life expectancy seven years below the national average (6, 7). Despite recent attention, health analyses for the Roma community have mainly been descriptive and quantitative, focusing on prevalent health issues, lifestyle factors, and healthcare access (8, 9). The new studies propose interventions addressing social contexts and cultural competence among healthcare professionals, yielding positive impacts on health indicators for minority communities (10, 11, 12).

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Czech literature also points to the overall deteriorated health status of the Roma minority, which is primarily influenced by an unsatisfactory social environment, but also by some cultural characteristics (13). The article also presents data from research carried out through a questionnaire survey among dentists and Roma over the age of fifteen (currently altogether 237 patients).

The dentists pointed out the low frequency of preventive visits among Roma patients, who most often visit the dentist only in the case of acute pain, and the general population has a low interest and adherence to dental care among this target group (14, 15).As previously mentioned, the Roma, also known as the Gypsy ethnic group, constitute a genetically isolated population with a shared origin, stemming from a limited number of "founders". The majority, reside in Europe, particularly in the Balkans and its southwestern regions. Roma individuals exhibit specific hereditary diseases, often stemming from recessive genetic mutations, with recent molecular-genetic investigations shedding light on several conditions prevalent within the Roma population.

Given the substantial Roma population in Europe, individuals with these genetic conditions may also be encountered in the Czechia. However, diagnosing such diseases proves challenging, leading to frequent underdiagnosis or misdiagnosis. Our research provides examples of autosomal recessive diseases, which can be molecularly confirmed, and prevalent within the local Roma community. These include in particular congenital cataract syndrome, facial dysmorphism and demyelinating neuropathy, non-syndromic prelingual deafness with *GJB2* (OMIM # 220290) impairment, and the myasthenic syndrome (16, 17, 18).

Seeman et al (16) and Lassuthova et al (17) described congenital Cataract Facial Dysmorphism and demyelinating Neuropathy syndrome (CCFDN, # OMIM 604468) which is based on an autosomal recessive multi-system disorder caused by the homozygous founder variant c.863+389 C > T in the *CTDP1* gene (#OMIM 604927). Thus far, there are 20 persons with this disease in the country.

Common symptoms observed in both groups included bilateral congenital cataracts and microphthalmia, often necessitating early cataract surgery. Diagnosis typically occurs around the age of two, with patients exhibiting varying degrees of delayed motor milestones. Notably, a paleocerebellar gait pattern was characteristic of all patients, with intellectual disability ranging between mild and variable.

Bouwer et al (19) reported a case of Congenital Cataracts Facial Dysmorphism Neuropathy Syndrome (CCFDN; #OMIM 604168), also attributed to a homozygous variant in the *CTDP1* gene, resulting in disruption of ribonucleic acid transcription machinery. This case involved a young Czech Gypsy female affected by the rare disorder, with the presence of the homozygous c.863+389 C>T variant in the *CTDP1* gene segregating within the family.

Brozková et al (20) described hereditary motor and sensory neuropathy-type type Lom (HMSNL; #OMIM 601455) which is also called Charcot-Marie-Tooth Disease, type 4D (CMT4D), caused by the homozygous founder variant p. Arg148* in the *N-Myc* downstream-regulated gene 1. Their study, identified HMSNL in 12 patients drawn from eight Czech families. Among these patients, 11 cases were attributed to the p. Arg148* variant inherited via autosomal recessive transmission from both parents, while one recessive variant was inherited solely from the father and revealed due to uniparental isodisomy of chromosome 8.

Furthermore, Bitner-Glindzicz et al (21) prepared a comprehensive review that Roma individuals exhibit specific hereditary diseases, primarily arising from recessive genetic mutations. The molecular-genetic mechanisms underlying these conditions have been recently elucidated, with several diseases prevalent within the Roma population confirmed at the molecular level. Examples include congenital cataract syndrome, facial dysmorphism and demyelinating neuropathy, non-syndromic prelingual deafness with *GJB2* gene impairment, and congenital myasthenic syndrome.

We aimed to monitor dental abnormalities in rare genetic diseases in the Czech Roma population which are treated in ERN CRANIO center in the Motol University Hospital of Charles University in Prague (www.em-cranio.eu). Since the Roma ethnicity is self-reported, the cases contained herein are based either on this subjective status or on pathogenic variants detected primarily in the Roma population elsewhere.

Overview of rare diseases which typically occur in the Czech Roma population and of typical symptoms in the area of the mouth

Congenital cataract: facial dysmorphism neuropathy syndrome (CCFDN; OMIM # 604168; ORPHA: 48431)

Disease definition

The rare autosomal recessive multiple congenital anomalies/dysmorphic syndrome is characterized by abnormalities of the eye; mildly dysmorphic facial features; and a hypo/demyelinating, symmetric, distal peripheral neuropathy.

The syndrome manifests itself in neurological problems, eye defects, and dental anomalies and has been found to occur exclusively in Roma cases with over 190 patients diagnosed thus far (21). CCFDN is a genetically homogeneous condition in which all patients are homozygous for the same ancestral variant in the *CTDP1* gene. *CTDP1* maps to 18qter and encodes a protein phosphatase whose only known substrate is the phosphorylated serine residues of the carboxy-terminal domain of the largest subunit of RNA polymerase II, indicating that CCFDN affects basic cellular processes of gene expression and developmental regulation. All the affected individuals are homozygous for the *CTDP1* Romani founder variant c.863+389 C>T.

Characteristic clinical features

- abnormalities of the eye (bilateral congenital cataracts, microcornea, microphthalmia, micro pupils);
- mild facial dysmorphism (prominent midface, thickening of the perioral tissues, forwardly directed anterior dentition, hypogonadism);
- developmental delay / mild intellectual disability;

- neuropathy – hypo/demyelinating, symmetric, distal peripheral;
- skeletal abnormalities (foot deformities, scoliosis as a result of muscle weakness);
- cerebellar involvement (ataxia, nystagmus, intention tremor, dysmetria);
- short stature and mostly subnormal weight;
- hypogonadotropic hypogonadism;
- para-infectious rhabdomyolysis – life-threatening complication.

Para-infectious rhabdomyolysis is a serious complication reported in an increasing number of patients. During general anaesthesia, patients with CCFDN require careful monitoring as they have an elevated risk of complications.

Typical symptoms appearing in the mouth area

The facial phenotype of Czech CCFDN patients: 9 children and adolescents:

- facial dysmorphism with prominent nasal philtrum;
- full lips;
- prominent incisors.

Treatment options

Prominent incisors and protruding lips can be corrected as part of dental orthodontic care and plastic surgery.

Oculofaciocardiodental syndrome (OFCD; OMIM # 300166; ORPHA: 2712) (Microphthalmia, Syndromic 2; MCOPC2)

Disease definition

Oculo-facio-cardio-dental syndrome (OFCD) is an ultrarare multiple congenital anomaly syndrome characterized by dental radiculomegaly, congenital cataract, facial dysmorphism and congenital heart disease. Among the rare genetic diseases primarily observed within the Roma population, to date, 20 cases have been reported worldwide (21). This syndrome follows an X-linked dominant inheritance pattern, transmitted through the female lineage. Given the absence of affected males, it is presumed that embryos affected by this syndrome are not viable. The *BCOR* gene (OMIM 300485) associated with this disease while its exact function remains unknown. Diagnosing OFCD can be particularly challenging due to its diverse array of symptoms. The syndrome can profoundly impact the quality of life, with prognosis contingent upon the severity of disability (Figs 1, 2). Its management requires appropriate cardiac, ophthalmic and dental care.

Characteristic clinical features

- ocular abnormalities (bilateral congenital cataracts, microphthalmia, regressive vision impairment, secondary glaucoma, ptosis, exotropia),
- facial dysmorphism (long narrow face, high nasal bridge, broad nasal tip with separated nasal cartilages, laterally curved and thick eyebrows, long philtrum, clefts of the hard/soft palate),

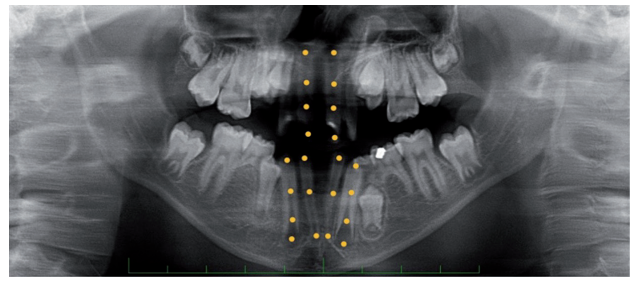

Fig. 1. Radiculomegaly (gigantism of tooth roots) of canines and the first premolars.

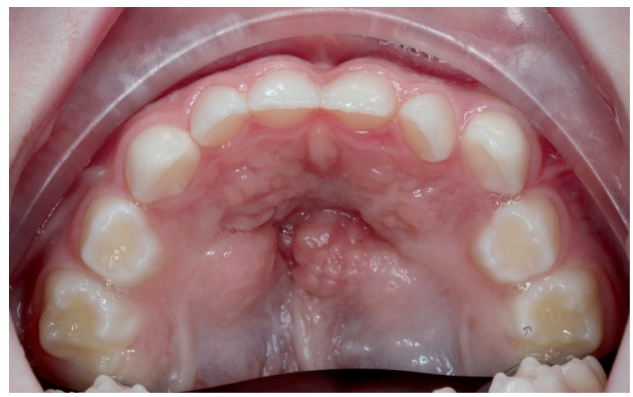

Fig. 2. Palatal cleft.

- cardiac defects (ventricular septal defect, atrial septal defect, mild cardiomegaly, ventricular and atrial hypertrophy, benign peripheral pulmonary stenosis, mitral valve prolapse),
- skeletal findings (syndactyly of the second and third toes, hammer-type flexion of the second and fourth toes, radio-ulnar synostosis, vertebral and rib anomalies),
- intestinal malrotation,
- hearing impairment,
- developmental delay / intellectual disability.

Typical symptoms appearing in the mouth area (16, 17)

- radiculomegaly (gigantism of tooth roots) of canines and sometimes even the first premolars;
- tooth roots can grow up to the level of the cortical plate of the orbit or mandible;
- hypodontia (Fig. 1);
- delayed development and growth of permanent dentition;
- cleft palate (Fig. 2).

Treatment options

Dental treatment focuses on individual, specific solutions to problems, and eventual dental and maxillofacial surgery procedures mainly:

- maxillofacial surgery
- braces or clear aligners; orthodontic appliances – e.g. palatal expander or reverse-pull face mask.

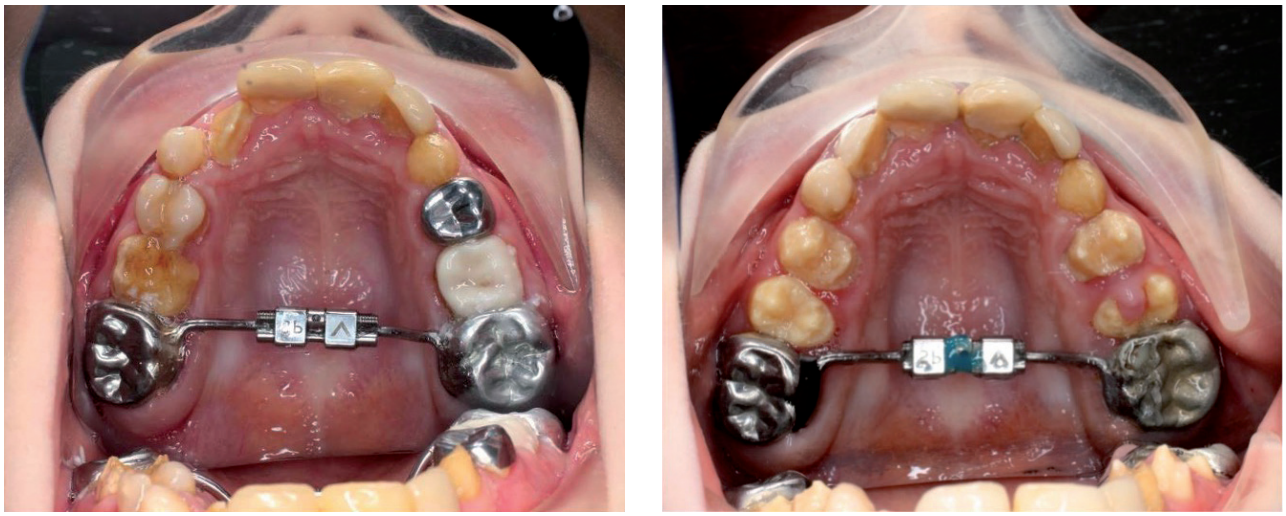

Fig. 3. Amelogenesis imperfecta – orthodontic therapy, NuSmile crowns, palatal expander. A. Start of therapy (2016). B. End of therapy (2017).

- Root gigantism can complicate orthodontic therapy, eye defects can cause impaired vision or even blindness and heart defects can have life-threatening consequences (Figs 1, 2).

Kohlschütter-Tönz Syndrome (KTZS) (Epilepsy-dementia-amelogenesis imperfecta syndrome; Amelocerebrohypohidrotic syndrome OMIM # 226750; ORPHA: 1946

Definition

The genetically heterogeneous autosomal recessive syndrome is characterized by the triad of amelogenesis imperfecta, infantile-onset epilepsy, intellectual disability with or without regression and dementia, is prevalent within the Roma population and is associated with mutations in the *ROGDI* gene (OMIM # 614574). This degenerative disease typically presents in newborns or at the latest in early childhood. Inheritance of the syndrome follows an autosomal recessive pattern, where both parents act as carriers, passing on the disease to their offspring without exhibiting clinical symptoms.

The progression and severity of the syndrome vary from individual to individual. While diagnosis historically relied solely on clinical manifestations, advancements in molecular genetic analysis now facilitate accurate diagnosis of this genetic condition.

Characteristic clinical features

- epilepsy / epileptic encephalopathy;
- developmental delay / intellectual disability severe to profound;
- other neurological findings (spasticity, hypertonia, ataxia, specific brain MRI findings);
- amelogenesis imperfecta;
- facial dysmorphism in some cases (microcephaly, coarse hair, mildly asymmetric skull, up-slanting palpebral fissures, smooth philtrum).

Typical symptoms appearing in the mouth area

- Amelogenesis imperfecta (Fig. 3): teeth are yellow to brown, which arises as a result of enamel damage;
- enamel is soft and insufficiently calcified;
- increased tooth decay and tooth deformation.

Treatment options

- First step: orthodontic therapy, e.g. NuSmile crowns, palatal expander (Fig. 3)
- In adulthood – prosthodontic or implant insertion

Cataract 11 with microphthalmia and neurodevelopmental abnormalities OMIM # 610623; ORPHA: 91492)

Definition

Variants in the *PITX3* gene (OMIM # 602669) cause multiple types of cataracts described, typical congenital total and/or posterior polar.

The *PITX3* gene encodes a transcription factor that is essential in the development of the anterior segment of the eye and the lens. So far, five unique variants in this gene have been described. They are associated with variable clinical courses at the level of individual families. Specifically, the c.640-656dup variant is the most common of them and is associated with the development of AD cataract with a large intrafamilial variability associated with dysgenesis of the anterior segment of the eye comprising cataract, congenital cataract, Peterson's anomaly and posterior embryotoxon. These birth defects occur unilaterally or bilaterally with variable onset from birth to adulthood.

Characteristic clinical features

- cataract;
- microphthalmia;
- Rieger anomaly;
- blindness.

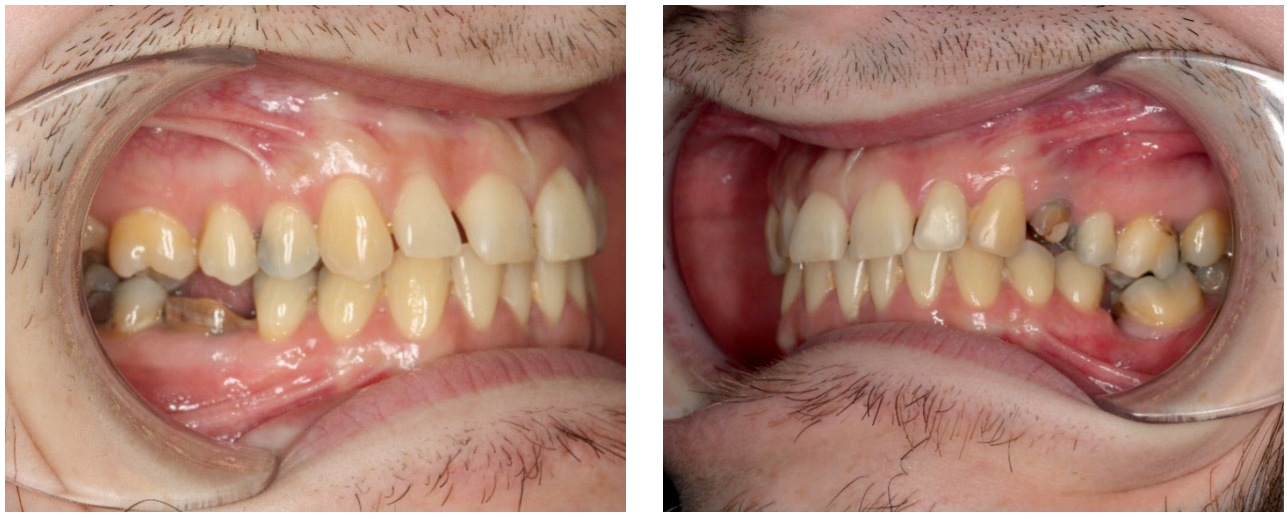

Fig. 4. Father- deformed dentition; high tooth decay. A. Right side. B. Left side.

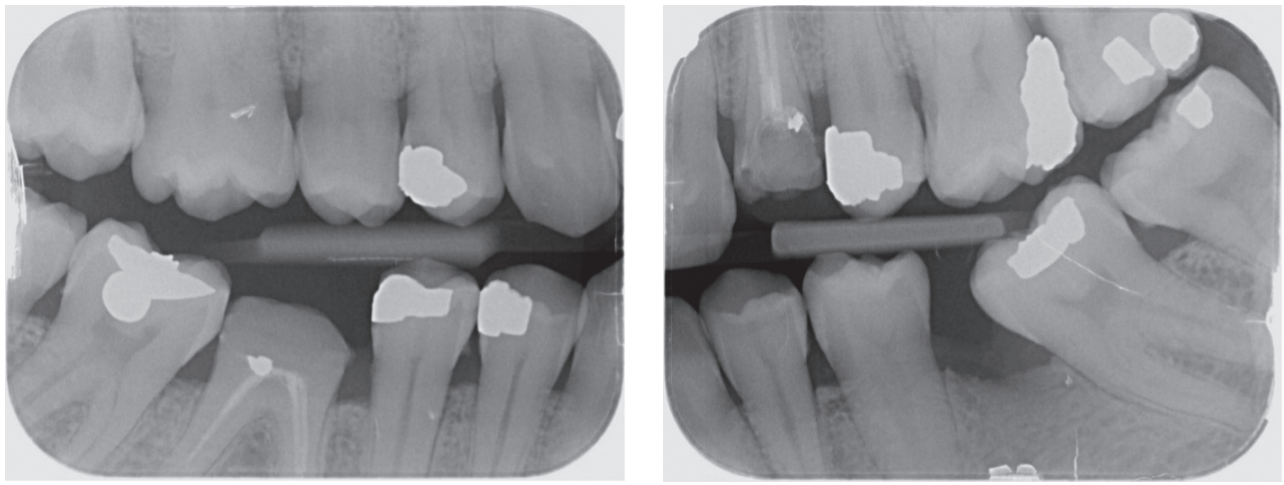

Fig. 5. Father – X-ray Images. A. Right side. B. Left side.

Typical symptoms appearing in the mouth area

- deformed dentition; high tooth decay (Figs 4, 5);
- anterior open bite (Fig. 6).

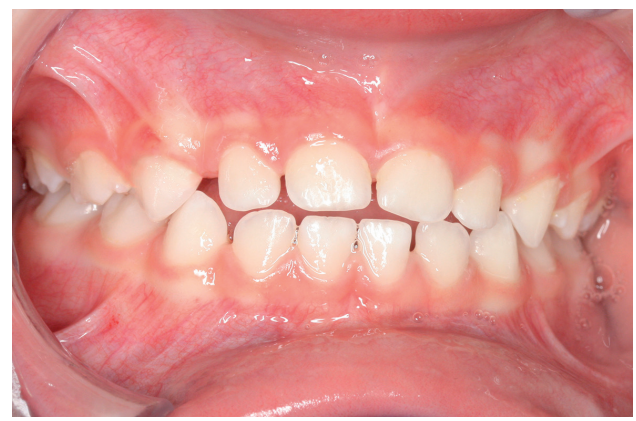

Fig. 6. Daughter- anterior open bite - upper and lower dental arch and smile line.

Discussion

The most comprehensive review dealing with Roma health issues was published by Zeman et al (22) who provided an overview of genetic and congenital anomalies, infectious diseases, nursing care etc. based on 129 articles. This review discussed complex genetic and congenital anomalies in a total of 5159 Roma patients from 19 nationalities. The most frequent were Roma cases in descending order of frequencies from Spain (1232), Hungary (1106), Bulgaria (761), India (756), Slovakia (251), and Czechia (34). Of the 129 articles only two studies by Edwards and Watt (23) and Edwards and Watt (24) focused on dental and oral hygiene. The first study included 43 individuals and the second study contained 115 persons. Given the findings of earlier genetic studies of Western European Roma (Irish Travelers) versus Eastern European Roma, it should be noted that this

study focused on a geographically small group and therefore may not be generalizable.

In our brief overview, we presented not only characteristic clinical features of four rare diseases common in the Czech Roma population but also typical symptoms appearing in the area of the mouth. Interestingly, the latter symptoms in the mouth area do not differ in the Roma cases from the mainstream population according to available information in the OMIM database or in available literature (25). The dental phenotypes in rare genetic bone diseases include four types of lesions: delayed tooth eruption, congenitally missing teeth, supernumerary teeth, and enamel hypoplasia. Importantly, the dental anomalies serve as "signal symptoms" for establishing the diagnosis of respective rare diseases. In our Czech Roma population, we found that amelogenesis imperfecta arises due to enamel damage with enamel being soft and insufficiently calcified. We also confirmed increased tooth decay and deformation, including the presence of cleft palate and various orthodontic anomalies.

Conclusions

In the case of ultrarare diseases, and in particular, in minorities, such as the Roma population it is often difficult to establish a clinical diagnosis and thus to start early therapeutic interventions. Although novel technologies, are used such as the application of artificial intelligence linked with human phenotype ontology, and three-dimensional facial scanning (26), the "dental phenotype" is often not considered a sentinel feature indicating further clinical and laboratory differential diagnostics. Knowledge of the dental phenotype is thus important and aids early therapeutic intervention and fosters orthodontic treatment planning (27). In summary, we provided a systematic review of dental phenotypes in ultrarare diseases commonly detected in the Czech Roma population which can indicate early therapy, including dental treatment. We also hope that this overview will aid the early diagnosis of these rare diseases when dental disorders are associated with other suspicious clinical features within the routine stomatological practice. Finally, this report fosters international collaboration in this regard within the ERN CRANIO consortium.

References

1. Fernández-Armesto F. Guide to the peoples of Europe. London: Times Books, 1994.

2. Duda P. Genomická studie poodhaluje původ a demografickou historii evropských Romů. Vesmír 92, 2013/4 193 based on Curr. Biol 2012; 22: 2342–2349.

3. Hajioff S, McKee M. The health of the Roma people: a review of the published literature. J Epidemiol Community Health 2000; 54 (11): 864–986.

4. Ramos-Morcillo AJ, Leal-Costa C, Hueso-Montoro C, Pino-Casado R., María Ruzafa-Martínez M. Concept of Health and Sickness of the Spanish Gypsy Population: A Qualitative Approach. Int J Environ Res Public 2019; 16 (22): 4492

5. Anderson LM, Adeney KL, Shinn, C, Safranek S. Community coalition-driven interventions to reduce health disparities among racial and ethnic minority populations. Cochrane Database Syst Rev 2015; 6: CD009905.

6. Horvat L, Horey D, Romios P, Kis-Rigo J. Cultural competence education for health professionals. Cochrane Database Syst Rev 2014; 5: CD009405.

7. Strategie rovnosti, začlenění a participace Romů (Strategie romské integrace) 2021–2030. 10. května 2021 vláda ČR schválila strategii rovnosti, začlenění a participace Romů 2021–2030.

8. Papadopoulos I, Lay M. The health promotion needs and preferences of Gypsy Travelers in Wales. Diversity in Health and Social Care 2007; 4: 167–176.

9. Broukal Z, Dušková J, Merglová V. Strategie prevence zubního kazu založené na důkazech. Část 3. Ústní hygiena v prevenci zubního kazu. Čes Stomat 2017: 117 (2): 35–42.

10. Rakosi T, Kozák F. Stav chrupu 2–6 ročných cigánských dětí. I. Kazivost dočasných zubov. Prakt Zub Lék 1958; 6 (1): 22–25.

11. Karásková P, Kajanová A. Romské obyvatelstvo a vybrané aspekty stomatologické péče. Čes Stomatol 2017; 117 (1): 8–12.

12. Bartosovic I. Some aspects of the health status of the Gypsy population in Slovakia. Bratisl Med J 2016; 117 (1): 26–30.

13. Karásková P. Informovanost romského obyvatelstva v oblasti stomatologické péče. Diplomová práce, Zdravotně sociální fakulta. České Budějovice: Jihočeská univerzita; 2016.

14. Nesvadbová, L, Šandera J, Haberlová V. Romská populace a zdraví: Česká republika – Národní zpráva; 2009.

15. Bučková M, Dostálová T, Kašparová M. Prevence a diagnostika zubního kazu v ordinaci praktického lékaře pro děti a dorost – stav chrupu pacientů ošetřených v celkové anestezii. Pediatr Praxe 2016; 17 (2): 65–69.

16. Seeman P, Sisková D. Autosomal recessive ethnic diseases of Czech Gypsies. Casopis Lek Ces 2006; 145 (7): 557–560.

17. Lassuthova P, Sišková D, Haberlová J, Sakmaryová I, Filouš A, Seeman P. Congenital cataract, facial dysmorphism and demyelinating neuropathy (CCFDN) in 10 Czech Gypsy children – frequent and underestimated cause of disability among Czech Gypsies. Orphanet J Rare Dis 2014; 9: 46.

18. Kalaydjieva L. Congenital cataracts-facial dysmorphism-neuropathy. Orphanet J Rare Dis 2006; 29 (1): 32.

19. Bouwer S, Angelicheva D, Chandler D, Seeman P, Tournev I, Kalaydjieva L. Carrier rates of the ancestral Indian W24X mutation in GJB2 in the general Gypsy population and individual sub isolates. Genet Test 2007; 11 (4): 455–458.

20. Šafka Brožková D, Laštůvková J, Štěpánková H, Krůtová M, Trková M, Myška P, Seeman P. DFNB49 is an important cause of non-syndromic deafness in Czech Roma patients but not in the general Czech population. Clin Genet 2012; 82 (6): 579–852.

21. Bitner-Glindzicz M. Hereditary deafness and phenotyping in humans. Br Med Bull 222.

22. Zeman CL, Depken DE, Senchina DS. Roma health issues: a review of the literature and discussion. Ethn Health 2003. 8 (3): 223–249.

23. Edwards DM, Watt RG. Oral health care in the lives of Gypsy Travellers in east Hertfordshire. Br Dent J 1997; 183 (7): 252–257.

24. Edwards DM, Watt RG. Diet and hygiene in the lives of Gypsy Travellers in Hertfordshire. Community Dent Health 1997; 14 (1): 41–46.

25. Iwata E, Sah SK, Chen IP, Reichenberger E. Dental abnormalities in rare genetic bone diseases: A literature review. Clin Anat 2023; 37 (3: 304–320.

26. Kováč P, Bražinová A, Varga I, Mrázik L, Aláč M, Smatana M, Thurzo A. Phenotyping Genetic Diseases Through Artificial Intelligence Use of Large Datasets of Government-stored Facial Photographs: Concept, Legal Issues, and Challenges in the European Union. Preprints 2023, 2023040344.

27. Thurzo A, Strunga M, Havlínova R, Reháková K, Urban R, Surovková J, Kurilová V. Smartphone-Based Facial Scanning as a Viable Tool for Facially Driven Orthodontics? Sensors 2022; 22: 7752.

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