

Autosomal Recessive Ethnical Diseases of Czech Roma Population

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ABSTRACT

The Roma people form a genetically isolated ethnic group of the same origin with an estimated worldwide population of 10-14 million, coming from a restricted number of the so-called founders. The majority (ca 8 million) of the members of the Roma ethnic group live in Europe, in particular in the Balkans and in the south-east of Europe. Among the Roma people there are specific diseases caused by the same recessive genetic mutation. Recently the basis of some diseases in the Roma population has been clarified on the molecular genetic level, and confirmed. Since there is a significant number of the Roma ethnic proportion in our population, Roma patients affected by these diseases may also be encountered in the Czech Republic. However, the diagnostics of these diseases is frequently a problem, and therefore these diseases are often under-diagnosed or not diagnosed correctly. Here are examples of autosomal recessive diseases, also confirmable also on the DNA level, which are found in the Roma in the Czech Republic: syndrome of congenital cataracts, facial dysmorphism and demyelinating neuropathy, non-syndrome pre-lingual deafness with the GJB2 gene disorder and congenital myasthenic syndrome.

Key words: syndrome of congenital cataracts, facial dysmorphism and demyelinating neuropathy; congenital myasthenic syndrome, non-syndrome pre-lingual deafness caused by the GJB2 gene mutations, founder, Roma, Gypsy.

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The Roma people are an ethnic population group of an estimated 10-14 million. The Roma represent a geographically scattered but still genetically isolated population originating from the restricted number of individuals, the so-called founders. The majority of the Roma people live in Europe, in particular in the Balkan countries and in the south-east of Europe. Unlike other populations, where systematic documentation and extensive genealogical records exist, the Roma ethnic group is characterized by a lack of reliable written records and by a nomadic way of life. Its origin is generally assumed to be in India. The anthropological, linguistic and historical records from the majority populations assume that the Roma people left India sometimes between the 5th and 10th centuries AD. In the 11th and 12th centuries they reached the Bysanthean area, and from there they moved to Europe from the southeast (1-3). A part of the Roma people who permanently settled in the Balkan – the area south of the Danube is specified as the Balkan Roma and the part continuing in the migration north from the Danube is specified as the Walachian (Olach) Roma (currently in Romania). Another part continued on the migration and settled further throughout Europe, thus reaching Slovakia and our territory as well. Most of the original Roma population of Bohemia were exterminated during the Second World War, and the current Roma people are mostly the descendants of immigrants from Slovakia and Bulgaria (4).

In various Roma groups living in different places in Europe, characterized by social and linguistic differences, specific and unique monogenetic recessive diseases have recently been described which are caused in the same group by the same mutation of the same gene based on the so-called founder's effect: hereditary

motor and sensory neuropathy of the Lom type in Bulgaria (HMSN-L) (MIM 601455) (5), congenital myasthenic syndrome (CMS) (MIM 608931) (6), syndrome of congenital cataracts, facial dysmorphism and demyelinating neuropathy (CCFDN) (MIM 604168) (7), LGMD2C (8) congenital glaucoma in Slovakia (9).

Some of these diseases are strongly bounded regionally, and their occurrence elsewhere is very rare. However, a number of hereditary diseases in the Roma people are caused by a disorder the origin of which is an old mutation which also exists in India, and therefore the physicians in all countries with the Roma population may be faced with these diseases – including a significant number in the Czech Republic

Some clinical units with typical occurrence exclusively or more frequently in the Roma people have been described only recently (for example CCFDN). The discoveries of the molecular causes of these diseases and of the causes of mutations, being mostly identical in the Roma, in the affected in the v homozygot condition demonstrate the common founder's origin of their emergence.

Some units are probably relatively frequent in the Roma population; however, in accordance with our existing experience they are not so familiar to Czech physicians, resulting in incorrect or unclear diagnostics in a number of those affected with the symptoms of some hereditary disorder typical for the Roma ethnic group. This was the reason for writing this summarizing article describing clinical symptoms, targeted diagnostics supporting examinations and the molecular cause of several autosomal recessive diseases we have repeatedly met in our clinics. Our opinion is that these disorders may be not so seldom in Czech patients of the Roma ethnic group. To our knowledge, these



Fig. 1. Examples of typical facial dysmorphism in patients with molecular genetically confirmed CCFDN syndrome. In the early childhood the face is not striking, and the dysmorphism is only typical in the age of adolescence. Typical are the slight ptosis of the lids, prominent lips, small chin and slightly prominent front teeth.



Fig. 2. Severe scoliosis of a severe deformities of legs and hands as a consequence of the peripheral neuropathy in a seventeen-year-old patient with a severe affection by the CCFDN

hereditary disorders have not been described in the Czech literature in recent years, and it may be that they have not been described there at all. In Slovakia, Prof. I. Bernasovský (10) has dedicated attention to the Roma problems and published works on the epidemiology in the Roma people.

SYNDROME OF CONGENITAL CATARACTS, FACIAL DYSMORPHISM AND OF DEMYELINISING NEUROPATHY

The syndrome of congenital cataracts, facial dysmorphism and demyelinating neuropathy (CCFDN) is a new unit described only in 1999 by Tournev in 50 Walachian Roma coming from 19 large families in Bulgaria (MIM 604168) (11). Subsequently patients were diagnosed and described in other European countries, including the Czech Republic (12). As with other diseases described here, this is an autosomal recessive hereditary disease with the CCFDN caused by the mutation in the *v* CTDP1 leading to partial deficiency of the carboxy terminal phosphatase domain 1



Fig. 3. Progressive peripheral demyelinating neuropathy in the CCFDN patients lead to secondary changes in muscles with the distal weakening and atrophy on the extremities.



Fig. 4. Typical ptosis (pictures on the left) in a patient with molecular genetically confirmed congenital myasthenic syndrome (homozygot for the 1267delG mutation in the *CHRNE* gene) a the retreat till deletion of the ptosis following the administration of the acetylcholinesterases blocker (pictures on the right)

(7). This enzyme has an important role in the CCFDN transcription process; therefore only after the discovery of the molecular cause was it classified in a small group of so-called transcription syndromes. Before the discovery of the causal mutation in the *CTDP1* gene some patients with CCFDN were repeatedly described as being affected by the Marinesco-Sjögren syndrome (MSS), due

to a similar combination of clinical symptoms. The finding of the IVS 6 + 389 C mutation to the T in the CTDP1 gene in patients of the Roma ethnic group with the MSS clinical diagnose of that time, along with the exclusion of this mutation and of other disorders of the CTDP1 gene in 19 patients with MSS who were not of Roma origin, meant that the hypothesis concerning the potential allelic origin of both diseases was excluded.

Clinical picture of CCFDN

The main symptoms are already present in the name of this disease. The clinical picture has some symptoms fully constant and present in all those affected, and some varying, present only in a few patients. The congenital cataracts, peripheral demyelinating polyneuropathy on the lower extremities after the 4th year of age, skeletal abnormalities including facial dysmorphism (Fig. 1) and the retardation of the psycho-motor development are constant symptoms. The scoliosis is present variably, affecting patients with CCFDN, in particular from the age of adolescence (Fig. 2), and the rhabdomyolysis after a viral infection has been described in these patients repeatedly. We have also noticed this in two patients of ours, in one of those repeatedly. The psycho-motor development in the CCFDN patients has always been retarded, and independent walking is possible in them only after the age of 3-4. The gait is always uncertain, on a wide basis, cerebellar, but also affected by the weakness of the lower extremities and by the polyneuropathy (Fig. 3). In these patients the conduction study on the EMG examinations shows a significantly decreased conduction velocity in the peripheral nerves of the lower extremities to the value of ca. 20 m/s after the 4th year of age, which remains stable later. In the nerves of the upper extremities these values are reached later, around the 8th year of age (13). In some CCFDN patients an acute, temporary rhabdomyolysis after a viral infection appears, when first the patients complain of major muscle or limb pains; later weakness made walking impossible, and there was temporarily also dark urine because of the macroscopic myoglobinuria. At the beginning the values of the CK, transaminases and of myoglobin in the serum reached the level of extreme values (CK even more than 500 kat/l, ALT and AST more than 10-15 kat/l, myoglobin more than 4000 kat/l) and returned to normal within ca. 3 weeks (14). Therapeutically, usually the fortified diuresis without any necessity of the dialysis is sufficient during this attack, which however should be always ready for the patient. At the adult age, or even before reaching it, the degenerative nature of this disease leads to invalidism, and life expectancy is most probably shortened; however, we have had no actual personal experience with a CCFDN patient older than 18 years yet.

CONGENITAL MYASTENIC SYNDROME (CMS) (MIM 608931)

This is a heterogenic group of diseases affecting the nerve-muscular transmission at all its levels, mostly caused by the inactivating autosomal recessive mutations, in particular of the following four genes: ChAT (cholin acetyltransferases) – presynaptic defect, COLQ (colagen domain of the subunit of the acetylcholinesterases) – synaptic defect, AChR (subunits of the acetylcholin receptor) or the RAPSN (rapsyn) gene – postsynaptic defects.

In the Roma CMS is most frequently caused by the disorder of the epsilon subunit of the AChR gene (CHRNE gene), and this in the prevailing majority by the 1267delG mutation in the homozygous condition, in the 2 exon of this gene (6). This mutation originated most probably in India ca 800–900 years ago, where it is relatively frequent in the population (15). The frequency of this so-

called founder's mutation in the Roma population in various parts of Europe is ca. from 0 to 8 % with the average of 3.74 % (15).

The clinical picture in Roma CMS patients caused by the homozygous mutation 1267delG has been relatively uniform, and from a young age it has typically included bilateral ptosis, striking fatigue, in particular of the eye-moving muscles, but also of the facial, swallowing and limb muscles (Fig. 4). Mostly the course has been stable and relatively benign and the condition and the patients' weakness typically has improved after administration of the acetylcholinesterases blockers (6) (Fig. 4). During the EMG examination in most patients decrement in repetitive stimulation has been recorded.

Non-syndrome pre-lingual deafness because of the GJB2 gene disorder

Loss of hearing and deafness are the most frequent sensory defects with the incidence in small children being of ca. 1:1 000 in various countries. Ca. 60 % of inborn or pre-lingual non-syndrome hearing loss is caused by a disorder of one of many genes. By far the most frequent genetically conditioned cause of inborn deafness are mutations affecting the GJB2 gene. As with other recessive diseases, in the GJB2 gene various prevalent mutations exist in different populations. The 35delG mutation is typical and prevalent for the European white population, being for example in the Czech Republic of more than 80 % of all pathogenic mutations of this gene (16). Probably deafness has had a higher frequency in the Roma population than in the Czech non-Roma population. However, systematic research and data are unfortunately still lacking. As established by Minárik et al. in Slovakia (17) and also observed and described by our team in Bohemia (16), and subsequently also for example in Spain (18), most deaf Roma are homozygotes for the W24X mutation, being prevalent in particular in India and Pakistan, these being the assumed origin of the Roma.

The level of the hearing loss in the homozygotes for the W24X mutation is very severe (usually of the 95–120 dB loss); this genotype has been connected with the most severe hearing loss, corresponding to the practical deafness in all affected known so far.

DISCUSSION

Currently, the Roma form an important part of our population. It is an ethnic group with an origin from a limited number of founders ca 32-40 generations ago (15), and as in other isolated groups, unique autosomal recessive diseases exist. Some diseases are based on old mutations which appeared in the original homeland of the Roma people, India, as is the case with CMS with the 1267delG mutation or the non-syndrome deafness with the W24X mutation. However, other diseases originated as consequence of mutations occurring later, only during the migration to Europe, as is the case with CCFDN, a disease connected only with the Roma ethnic group. The genetic homogeneity of this ethnic group can be assumed to have simplified the acceleration of the molecular genetic testing, and thus simplification of the whole diagnostic process; however, for a physician familiar with these problems and diseases that otherwise either exist very seldom (CMS) not at all in the majority population (CCFDN). However, there are also diseases which are usual in our majority population and also occur in the Roma, though mostly based on the specific mutation, such as for example with phenylketonuria (PCU) or neuronal ceroidlipofuscinosis (NCL).

Due to the ethnic origin, the clinical and molecular diagnostics of these diseases regarding diagnostic considerations should not be of a problem for an informed physician.

With CCFDN, where the congenital cataracts has been present in

all patients already birth and these patients have undergone eye cataract surgery very early, there is an ideal precondition: providing agreement and interdisciplinary cooperation between the paediatric neonatologists, ophthalmologists and paediatric neurologists and geneticists, the nationwide and complete capture of this serious neurodegenerative disease would be possible. The affected families would be provided with an efficient, timely genetic prevention by means of pre-natal diagnostics, and the affected patients would be given corresponding symptomatic treatment. Further, timely and correctly targeted diagnostics of these ethnically specific diseases would undoubtedly lead to significant savings, considering unnecessary complicated and often invasive examinations performed on the patients, in our experience, due to insufficient information and experience of the physicians concerning the diseases of this ethnic group. In future, a specialized genetic outdoor department for patients and families of the Roma origin might simplify and rationalize the diagnostics of the genetic disorders of this ethnic group. Regarding the fact that ca. every 8-10 Roma is a carrier of at least one of five recessive mutations as for the CMS, CCFDN, HMSN-L, GMD2C (girdle muscular dystrophy of the 2C) type or of the GALK1 (deficit of the galactokinase (15), it is clear that this fact presents a big health threat for the members of this ethnic group and that, for example, a preventive program of testing the most frequent recessive mutations for the members of this ethnic group might be very beneficial, as it was the case in Slovakia regarding the mutation for the congenital glaucoma. The DNA chip development for testing of the most frequent mutations in a large proportion of the population might facilitate this program in near future and allow significant price savings.

Abbreviations

CCFDN – congenital cataracts, facial dysmorphism and demyelinating neuropathy syndrome
 CMS – congenital myasthenic syndrome
 GALK1 – deficit of the galactokinase
 HMSN-L – hereditary motorical and sensitive neuropathy of the Lom type
 GMD2C – girdle muscular dystrophy of the 2C type
 MSS – Marinesco-Sjögren syndrome
 NCL – neuronal ceroidlipofuscinosis
 PCU –phenylketonuria

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Comments to the Article by Seeman P. and Šišková D. “Autosomal Recessive Ethnic Diseases in the Czech Gypsy Population”

The identification of high-risk population groups for selected hereditary conditioned diseases with serious clinical courses and unfavorable prognosis, timely diagnosis of individual diseases in concrete patients, and – primarily – genetic consultation of families that are at high risk for fetal abnormalities, are among the most effective preventive medical programs in medical, ethical, and economic terms.

The development of new molecular-biological methods, including “chip technologies” and methods using “gene mapping”, has contributed significantly to the understanding of the molecular and biochemical characteristics of a number of diseases with previously unknown etiology (1, 2).

It has been known for some time that the occurrence of some hereditary conditioned diseases may differ significantly between certain populations. For example, classic phenylketonuria has an occurrence of cca. 1:4500 in Northern Ireland, 1:10 000 in the Czech Republic, 1:50 000 in African-Americans, and 1:77 000 in China, while the occurrence of Gaucher’s disease is cca 1:60 000 in western Europe, cca. 1:100 000 in the Czech Republic and 1:500-2000 in the Ashkenazi Jews in the US and in Israel.

Practical medical experience must include knowledge of regional differences in the occurrence of some diseases. The article by P. Seeman and S. Šiškové, dealing with the problems of three autosomal recessive diseases in the Gypsy population, indicates that the Gypsies present – not only in the world at large but also in the Czech Republic – a complex population with significant internal stratification, particularly regarding the increased risk of occurrence of some genetically conditioned diseases as compared to other population groups (3).

Approximately 10 million Gypsies are living in Europe, representing an ethnic group with a common origin. Their “specific life style”, as well as a significant “social and economic pressure” lead to a continuous fragmentation of the Gypsy community in Europe and to the formation of “genetically and geographically” different sub-isolates (4, 5). Because of the lack of written historical documents concerning the life of the Gypsies, however, little reliable demographic data exists – in contrast to other population groups in Europe. Neither the higher occurrence of some diseases in the Gypsy population generally, nor the phenomenon among Gypsies living in a “smaller region”, in comparison with the occurrence of the same disease in other population groups, has been clarified to date. By means of mathematical models using the result of the targeted molecular analyses and genetic mapping, the original Gypsy population in the whole of Europe seems to have been founded cca. 32–40 generations ago, whereas various occurrences of some diseases in the current Gypsies may be connected with “founders’ mutations” (the founder effect), having arisen in their families cca. 16–25 generations ago (4).

The study of specific health problems in the Gypsies has become increasingly important. No region’s health system should “marginalize” the specificity of some aspects of the health problems in smaller population groups, because lack of information concerning the causes of some diseases might lead not only to insufficient clinical experience with the disease, but also to a subsequent increase in the financial costs of the health and social care. Only adequate knowledge about the existence of hereditary conditioned diseases will contribute to a better diagnostics of the patients with specific hereditary conditioned diseases and to the improvement of conditions for secondary genetic prevention.

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