



## CASUISTIC PAPER

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# A 16-year-old patient with Charcot Marie Tooth disease in variant c.217G>C of the *INF2* gene and focal glomerulosclerosis – a case report

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## ABSTRACT

**Introduction.** Charcot Marie Tooth disease (CMT) is currently one of the most commonly diagnosed and commonly hereditary sensorimotor neuropathies. Concluding from the literature, this is the first study describing the case of a patient with CMT disease in the c.217G> C variant of the *INF2* gene and focal segmental glomerulosclerosis.

**Aim.** To present a case of a 16-year-old patient suffering from CMT disease in variant c.217G> C of the *INF2* gene and focal glomerulosclerosis.

**Description of the case.** The text describes the CMT disease in a patient who underwent the WES / WGS-NGS genetic test and found a mutation within the *INF2* gene at the chromosomal position hg38 14: 104701582-G> C, cDNA level c.217 G> C, notation at the p protein level (Gly73Arg). Genotype record according to Human Genome Variation Society: NM\_022489.4: c.[217G> C]; [217 =]. The publication includes data on genetics, molecular mechanisms of the disease, diagnostic methods, rehabilitation and surgical treatment.

**Conclusion.** CMT disease is a heterogeneous group of diseases caused by mutations in various genes. The incidence of this pathology has increased significantly in the last century. Currently, there are no treatments available to combat this disease, and symptomatic treatment is the only treatment available.

**Keywords.** exome sequencing, neuropathy, nephropathy

## Introduction

Charcot Marie Tooth disease (CMT) is currently one of the most commonly diagnosed and commonly hereditary sensorimotor neuropathies.<sup>1</sup> It is a heterogeneous

group of genetic disorders characterized by dysfunction of peripheral nerves. It leads to limitations of motor activity, reduction of muscle tone, loss of tendon reflexes, progressive symmetrical atrophy of the distal muscles of

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the lower limbs and feet. Sequentially it affects the upper limbs, ultimately causing atrophy of the optic nerve.<sup>2-5</sup> The observations so far indicate a positive correlation between the length of the nerve fiber and the sequence of its involvement, leading to the involvement of the longest nerve fibers in the first place.<sup>1</sup> The development of the disease is associated with many other complications leading to limit independent activity and reduce fitness, both in terms of movement and sociology. The clinical features of CMT are pain, deformity, and disability, however, these are dependent on the type of CMT.<sup>6</sup> There is no approved pharmacological treatment at the current stage of research.<sup>7</sup>

CMT classification is based on the average nerve conduction velocity and is divided into three types: CMT type 1 also known as demyelinating, intermediate CMT and CMT type 2, which is dominated by axonal injuries.<sup>5-8</sup> CMT type 1 is characterized by significantly reduced speeds of the motor nerve (below 38 m/s) as well as segmental demyelination and remyelination with bulbous formations visible in the histological image. histological image.<sup>9</sup> In contrast, in the intermediate CMT, the velocity is 25-45 m/s.<sup>8</sup> Currently, there are three types of inheritance: autosomal dominant, autosomal recessive and X-linked.<sup>10</sup> with autosomal DI-CMT, while GJB1 is associated with X-linked DI-CMT.<sup>11,12</sup>

Formins are a family of proteins whose main task is to create linear actin polymers. Formin INF2 and its mutations have been found to be a major factor in the development of focal segmental encephalopathy (FSGS), which leads to glomerular degeneration, resulting in end-stage chronic kidney disease.<sup>13</sup> The INF2 gene encodes formin, which reacts, among others, Rho-GTPase CDC42 and the MAL protein responsible for the

structure of lymphocytes as well as myelination and its proper maintenance.<sup>14</sup> Various actin binding processes are modulated by proteins, including formin. Formin use, among others FH2 (formin homology 2) being the domain of creating new filaments that remain on the hooked end until the elongation process is complete.<sup>15,16</sup> FH1 (formin homology 1) accelerates elongation through its interaction with profilin.<sup>17</sup>

Concluding from the literature, this is the first study describing the case of a patient with Charcot Marie Tooth disease in the c.217G> C variant of the INF2 gene and focal segmental glomerulosclerosis.

### Aim

To present a case of a 16-year-old patient suffering from CMT disease in variant c.217G> C of the INF2 gene and focal glomerulosclerosis.

### Description of the case

This paper describes the case of a 16-year-old female patient, white. The second pregnancy was normal, terminated by caesarean section, with a birth weight of 3250 g, the second birth, the newborn scored 9 points on the Apgar scale. Development in the neonatal period was normal. At the age of 5 months, an ultrasound examination was performed, which gave the following results: heart positioned correctly, venous inflow and the size of the heart cavities normal, atrioventricular closed joints, continuous interatrial septum, normal thickness and systolic function of the left ventricular muscle, arterial openings normal and their diameter and flow velocities remained normal, normal left-sided aortic arch, normal flow in the abdominal aorta, echo from the endocardium and pericardium was normal. Based on the



Fig. 1. Deformed, shrunken fingers

above-mentioned description, no anatomical and functional abnormalities were found. Additionally, the examination did not reveal any abnormalities in the structure of the kidneys. The child walked a year ago, developing according to the norms. From about the second/third year of life she showed a tendency to walk on tiptoes, this symptom developed through foot drop, weakening of the distal muscles, especially of the lower limbs, until the onset of contractures. As the disease progressed, the patient developed a wading gait.

At the age of seven, during hospitalization, an EMG examination was performed, which showed the features of mixed, axonal-demyelinating neuropathy, then he was diagnosed with congenital motor-sensory neuropathy, the speed of conduction in the motor fibers of the median nerve was 29.3 m/s, in the ulnar nerve, conduction at the speed of 30.7 m/s, the peroneal nerve responded only to the tibial nerve, no sensory responses from the median, ulnar and sural nerves, and a record from the tibial muscle with features of chronic reinnervation. Additional tests revealed an increased TSH value (12.6 IU/ml) and an endocrinological consultation was recommended. Rehabilitation began.

At the age of 14, ultrasound of the thyroid gland and abdominal cavity was performed, which gave the following results: thyroid located in a typical site, nodule and both lobes of homogeneous echogenicity, in the left lobe and nodule without focal changes, a focal change visible in the right lobe. A 3.5 mm thick wick left and right lobes with the correct dimensions. In the middle part of the right lobe, near the posterior contour, there is an oval focal lesion with reduced echogenicity compared to the thyroid gland, with a diameter of 7 mm vascularized from the periphery. Cervical lymph nodes without signs of enlargement. Liver not enlarged, without echogenicity disturbances, thin-walled gallbladder without deposits present, common bile duct and portal vein not dilated. The area of the pancreas of homogeneous echogenicity, not dilated, without focal changes. The abdominal aorta is normal, the peri-aortic and retroperitoneal spaces are free. Both kidneys have the correct position, size, improper differentiation of the cortical spinal cord, no clear boundaries between the cortical and medullary parts with the hyperechoic cortical part, no focal changes.

The right kidney measures 107 mm/42 mm, the left one measures 98 mm/50 mm. Adrenal glands free. Spleen of homogeneous echogenicity and not enlarged, smooth-walled bladder.

In October 2019, during hospitalization due to incorrect values of outpatient tests of kidney function parameters, slight swelling of the face was found on physical examination. In a history of several months, periodic swelling of the eye area, the tests performed confirmed the high values of urea, creatinine and po-

tassium. Moreover, anemia and biochemical indicators of disturbances in the functioning of calcium and phosphate metabolism were found. Hemodialysis was performed. The treatment was prescribed furosemide, calcium preparations and active vitamin D3. Due to the high blood pressure, amlodipine was administered. During hospitalization, the patient required regular hemodialysis treatments. Despite the implementation of erythropoietin and iron, there was a need for transfusion of the erythrocyte mass twice. Urine red blood cells and urine proteins (3.6 g/day) were present in the urine all the time. With a slightly reduced level of protein and albumin in the blood. During the same hospitalization, a biopsy was also performed, the complication of which was an ultrasound-controlled retroperitoneal hematoma. Before the biopsy results were obtained,



Fig. 2. Deformed toes

immunosuppressive treatment was attempted, unfortunately without any therapeutic effect. The biopsy results confirmed the irreversible nature of the kidney damage: the biopsy covers the cortical and medullary parts of the kidney, contains up to seven glomeruli, almost all of them completely or almost completely sclerotized. Remains of postcapillary hyperplasia were found within the glomeruli. The dilated, fibrotic stroma contains chronic inflammatory infiltrates, numerous atrophic tubules, and numerous vitreous cylinders. Negative amyloid reaction. Immunofluorescent moderately abundant peripheral IgG deposits, C3c irregular deposits, copious irregular IgM deposits, trace fibrinogen deposits. Ultrastructurally enhanced glaz-

ing features. The changes present in the biopsy correspond to chronic advanced nephropathy, possibly crescent-forming glomerulopathy. A cardiological consultation was also performed, during which secondary left ventricular hypertrophy was found. During the neurological consultation, it was found that it was impossible to induce deep reflexes from the lower limbs and a weakly expressed deep reflex from the upper limbs, as well as hollow feet, deformed toes, drooping feet, and stork gait. After discharge, hemodialysis continued and genetic testing was suggested. At a later stage, a permanent catheter was also inserted.

In September 2020, the patient was admitted to a genetic clinic. WES/WGS-NGS genetic test was performed. The proband's parents and sister were also examined. The test sample showed a mutation within the *INF2* gene at the chromosomal position hg38 14:104701582-G> C, cDNA level c.217 G> C, and p. Protein (Gly73Arg). Genotype record according to Human Genome Variation Society: NM\_022489.4: c. [217G> C]; [217 =]. The above-mentioned variant in the *INF2* gene was not found in the father and sister. Two different nucleotides in the c.217G> C position of the *INF2* gene were found in the patient's mother, which suggests a possible low-percentage mosaic pattern for the variant studied. Pathogenic *INF* gene variants are responsible for Charcot Marie Tooth diseases and/or focal segmental glomerulosclerosis in an autosomal dominant model of inheritance.

## Discussion

Molecular understanding of disease is very difficult, but medicine is advancing, making the possibility of targeted therapy emerging, but it is an extraordinary challenge.<sup>18,19</sup>

Charcot-Marie-Tooth disease (CMT) indicates a genetically heterogeneous group of primary genetic neuropathies classically with sensory and motor involvement, referred to as hereditary sensory and motor neuropathy (HSMN).<sup>18</sup> CMT is the most common hereditary disease of the peripheral nerves in the world with a frequency of 1:2500.<sup>18</sup>

Pain in CMT patients is frequent, frequent, and has a strong impact on patients, however, it is difficult to classify as the literature data are inconclusive, suggesting either a biomechanical or neuropathic pathomechanism.<sup>19,20</sup> Early treatment in physical medicine and rehabilitation of patients with Charcot-Marie-Tooth disease is essential to reduce the sequelae of the disease and slow its progression.<sup>21-23</sup>

Knowledge of Charcot-Marie-Tooth disease (CMT) has grown significantly in recent years. It is an increasingly common disease as the spread of defective genes associated with it increases among the population (around 10-28/100,000). Due to the development of new studies on this disease, more and more genes are

identified with it, which significantly hinders its classification.

One of the publications of Spanish researchers from the La Fe University Hospital in Valencia describes a case of surgical treatment of CMT symptoms. The study included 16 patients, mainly women (62.5%) with the CMT1A phenotype (62.5%) with an average age of 39.5 years. In 13 patients, Achilles tendons were surgically lengthened, interphalangeal arthrodesis and plantar fascia dissection were performed. Two of them required additional ankle arthrodesis (due to its persistent varus) and extension of the long toe extensor. Patients were followed for an average of 42 months. 75% of patients assessed the effect of the surgery as "excellent" or "good". This study showed that the above-mentioned surgical techniques show high therapeutic efficacy and a high level of patient satisfaction.<sup>24</sup>

Another study was to test the effectiveness and safety of suppression of the *PMP22* gene, duplication of which in Schwann cells is one of the causes of Charcot-Marie-Tooth 1A disease (CMT1A). For this, a recombinant AAV serotype 9 (AAV2/9) vector was used, which introduces GFP and shRNAs (targeting *Pmp22*mRNA) and causes their expression in the recipient organism. This vector was injected into the sciatic nerve of animal models of the disease (mice, rats, and non-human primates). This treatment resulted in the recovery of the expression level of the *PMP22* gene to normal, which resulted in increased myelination of peripheral nerves. This effect prevents motor and sensory impairment in rat CMT1A models.<sup>25</sup>

Based on research from the Department of Neuro-Orthopedic Rehabilitation of the Rothschild Hospital, Assistance Publique-Hôpitaux de Paris, it has been found that early treatment and rehabilitation of patients with Charcot-Marie-Tooth disease is essential to reduce symptoms and slow the progression of the disease. Before starting therapy, the extent of neurological disorders, deficits in muscle tissue and joints should be clinically assessed, and then an individual rehabilitation program should be established for each patient. The condition of patients with this condition can be assessed through a number of different tests, including balance assessment on a stabilometric platform and gait assessment. In the rehabilitation of such people, e.g. cycloergometers (for lower limb exercises), treadmills (gait estimation, fatigue calibration and endurance training), isokinetic machines (training quadriceps muscles, hamstrings, extensors and spinal flexors), orthoses for gripping and training hand muscles. Such therapy enables patients to maintain physical and manual fitness and ensures independence in everyday life, which significantly improves their comfort and quality of life.<sup>21</sup>

CMT is associated with kidney disease in many sources, so a study was conducted to test the hypothesis

that mutations in the *INF2* gene (indirectly involved in nerve myelination) may be responsible for Charcot-Marie-Tooth neuropathy in the course of focal segmental glomerulosclerosis renal function (FSGS). For this purpose, direct *INF2* genotyping was performed in sixteen CMT and FSGS patients who had no mutations in the *PMP22* and *MPZ* genes. Of these individuals, 12 had mutations in exons 2 and 3 coding for *INF2*. During immunohistochemical analysis, strong expression of this gene in Schwann cells was demonstrated. Mutant *INF2* genes disrupted the *INF2*-*MAL*-*CDC42* pathway involved in important steps in myelination. These results suggested that *INF2* may be responsible for diseases of the glomeruli and the peripheral nervous system.<sup>14</sup>

Despite the holistic approach offered by the study of the clinical exome, the molecular tools available today guarantee the possibility of analyzing about 80% of target genes. Additional analyzes are necessary to verify the nature of the identified lesions, in this case the study of mosaicism in the patient's mother and the detection of genetic variants that could explain the cause of the observed disease.

Charcot-Marie Tooth disease is associated with a wide spectrum of different peripheral neuropathies. They affect the sensory and motor nerves, they cause muscle atrophy. At the moment, patients with this disease can be treated with rehabilitation and corrective surgery. Research is carried out on the mouse CMT-1A model to check the effectiveness of ascorbic acid. Research has shown that ascorbic acid decreased *PMP22* expression to a level below what is needed to induce disease. As ascorbic acid has shown therapeutic efficacy for patients with Charcot-Marie Tooth disease, it has been approved by the FDA.<sup>26</sup> Different muscles are attacked at different stages of disease progression. When the activity of one muscle weakens, the antagonist defeats it and, as a consequence, deforms. The main purpose is to reduce the action of the forces that cause the deformation. Minimally invasive procedures include plantar fasciotomy, Achilles tendon lengthening, transfer of the long fibula to the fifth metatarsal bone.<sup>27</sup> To improve the functions of the hand areas, a tendon transfer procedure is used in clinical practice.<sup>28</sup> To prevent joint contracture, use orthoses and rehabilitation that will improve the functioning of the patient. In clinical treatment, bone operations are also performed, e.g. osteotomies and joint fusions.<sup>29,30</sup>

## Conclusions

Charcot Marie Tooth disease is a heterogeneous group of conditions caused by mutations in different genes. The course of the disease is variable due to genotypic and phenotypic heterogeneity. The incidence of this pathology has increased significantly in the last century, which is related to the dynamic and rapid development

of medicine in the field of clinical genetics. Currently, there is no pharmacotherapy for Charcot-Marie-Tooth disease, and the only treatments available are rehabilitation and surgery for skeletal deformities, although best practices have not been identified. However, patients in Poland can increasingly count on the help of specialists involved in the treatment of diseases related to the human genome. This commitment gives hope for the improvement of patients' clinical condition and psychomotor and social functioning.

## Declarations

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### Author contributions

Conceptualization, M.P., D.M., M.J., A.S., K.R., J.W., A.P.; Methodology, M.P., D.M., M.J., A.S., K.R., J.W., M.R., J.K., R.P., D.A., A.P.; Validation, M.P., D.M., M.J., A.S., K.R., J.W., M.R., J.K., R.P., A.P., D.A.; Formal Analysis, M.P., D.M., M.J., A.S., K.R., J.W., M.R., J.K., R.P., D.A. A.P.; Investigation, M.P., D.M., M.J., A.S., K.R., J.W., M.R., J.K., R.P., D.A., A.P.; Resources M.P., D.M., M.J., A.S., K.R., M.R., J.K., R.P., D.A., A.P.; Data Curation, M.P., D.M., M.J., A.S., K.R., M.R., J.K., R.P., D.A., A.P.; Writing – Original Draft Preparation, D.M., M.J., M.P., A.S., K.R., J.W., D.A.; Writing – Review & Editing, D.M., M.J., M.P., A.S., K.R.; Visualization, M.P., D.M., M.J., A.S., K.R., J.W., M.R., J.K., R.P., D.A. A.P.; Supervision, A.P. and D.A.

### Conflicts of interest

The authors declare no conflict of interest.

### Data availability

Further enquiries can be directed to the corresponding author.

### Ethics approval

Informed consent was taken from the patients.

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