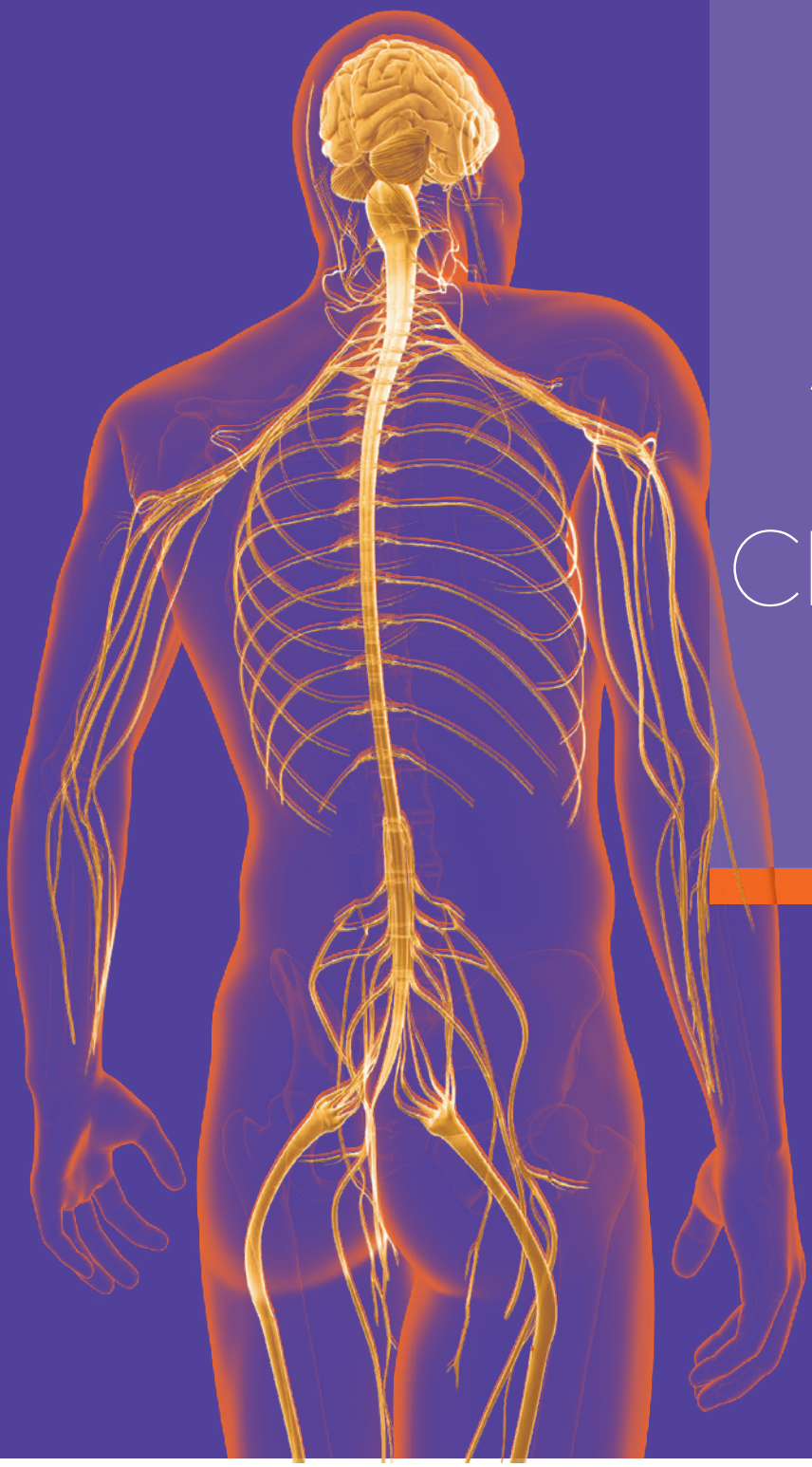


DYSIMMUNE INFLAMMATORY PERIPHERAL NEUROPATHIES

A PUBLIC HEALTH CHALLENGE

Press Kit
June 2024

ABOUT 1.3 MILLION PATIENTS AFFECTED WORLDWIDE

EPODIN
European Patients Organization for Dysimmune & Inflammatory Neuropathies

Deutsche GBS CIDP Selbsthilfe e.V.

AFNP

CIDP ITALIA onlus

GBS|CIDP polineuropatías inmunomediadas

A.R.B.N.P.

gain

TABLE OF CONTENTS

PRESS CONTACT EUROPE
Patrizia Garzena (communication@epodin.org)

CONTACT EPODIN
EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES
Jean-Philippe Plançon, President of EPODIN (jean-philippe.plancon@epodin.org)
Tel: +33 686 962 511

PRESS KIT PRODUCED BY EPODIN

Akkanto Paris

Staying autonomous and recovering mobility are possible !

DYSIMMUNE INFLAMMATORY PERIPHERAL NEUROPATHIES

A PUBLIC HEALTH CHALLENGE!

Decrease of health-related quality of life, loss of opportunity, inequality of care, social and professional exclusion mark the daily lives of many patients suffering from dysimmune inflammatory peripheral neuropathies (DIN) around the world.

A patient can spend up to 16 years wandering before being diagnosed with the right disease. This long journey in many cases is followed by a wandering for adequate treatment. Thus, an additional difficulty is the lack of sufficient supplies of plasma-derived medicines, (indicated and validated treatment in many cases of DIN) which means that some patients have to resign themselves to degraded care. This is an intolerable and little-known situation.

The European patient organization EPODIN* has made its priority to put an end to this public health challenge and to work with all stakeholders (Research, rare disease networks, industry, health professionals...) to find effective and sustainable solutions for patients.

In this spirit, EPODIN launch the Day for Dysimmune Inflammatory Peripheral Neuropathies on **11 June 2024**: the DIN DAY** to raise awareness of these little-known diseases and to give every citizen suffering from a dysimmune inflammatory peripheral neuropathy the opportunity to reduce the burden of his or her disease and the inequalities it causes, regardless of their social status.

** EPODIN: European Patient Organisation for Dysimmune and Inflammatory Neuropathies.*

*** International day dedicated to Dysimmune and Inflammatory Neuropathies (DIN)*

JEAN-PHILIPPE PLANÇON,
President of EPODIN

"Imagine that you gradually lose the use of your hands, arms and legs, and that everyday actions that are usually harmless, such as moving around, feeding yourself or dressing yourself, become difficult or impossible to perform. This is what I experienced since the age of 30, as, unfortunately, nearly 1.3 million people worldwide affected by dysimmune inflammatory peripheral neuropathy.

Many people are familiar with Guillain-Barré syndrome, the most acute form of dysimmune inflammatory peripheral neuropathy (DIN). This syndrome can lead to total paralysis within a few hours and in some cases to intensive care unit when the respiratory muscles are affected. It is still fatal for a significant number of patients.

The chronic forms of DIN such as chronic inflammatory demyelinating polyneuropathy, Lewis-Sumner syndrome, multifocal motor neuropathy, or neuropathy associated with monoclonal gammopathies are almost totally unknown to the general public.

Today, there is no curative treatment and many forms of DIN do not have any treatment at all. Fortunately, symptomatic treatments, such as plasma-derived medicinal products (PDMPs), exist but they suffer dramatic shortages for patients. Beyond treatment, fundamental research is still very limited.

DIN DAY, an international day dedicated to dysimmune inflammatory peripheral neuropathies is a wonderful opportunity to raise awareness among the general public, to support research and to mobilise the community of patient organisations that, all year round and all over the world, help patients and their families in their journey.

A PUBLIC HEALTH CHALLENGE

1

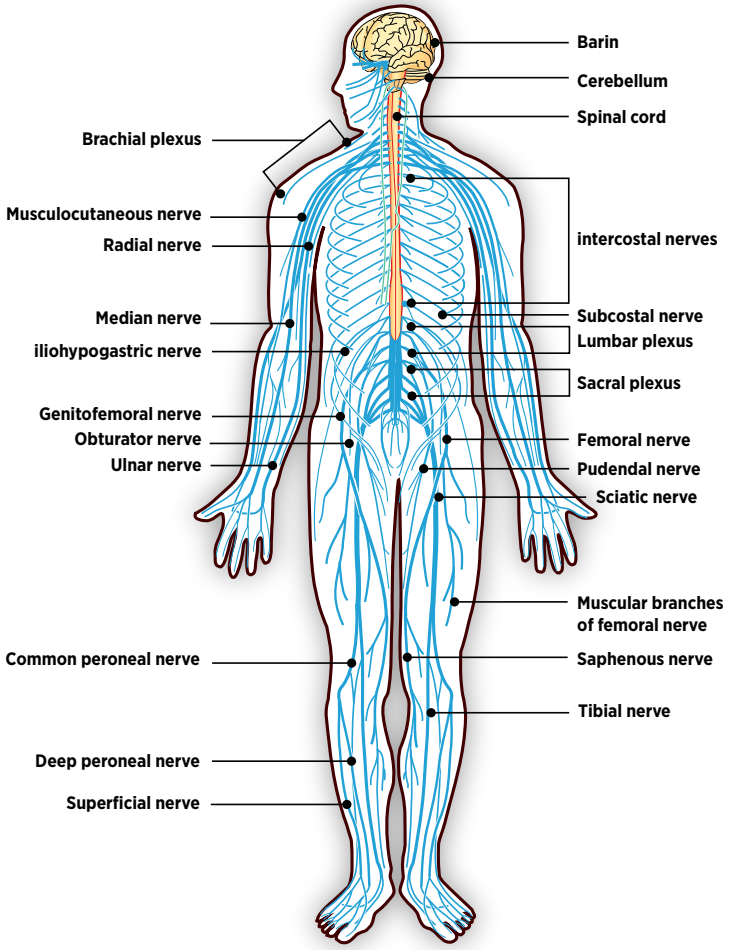
DIAGNOSTIC WANDERING: THE DIVERSITY OF PATHOLOGIES AND SYMPTOMS MAKE DIAGNOSIS AND TREATMENT DIFFICULT

Dysimmune inflammatory peripheral neuropathies are characterised by damage to the peripheral nervous system. The peripheral nervous system refers to **parts of the nervous system outside the brain and spinal cord.** It includes the cranial nerves, spinal nerves and their roots and branches, peripheral nerves, and neuromuscular junctions.

DIN are very disabling. They cause muscle weakness, numbness, tremors, balance troubles, severe fatigue and pain. All the symptoms depend on the location, the area (axon, myelin, node of Ranvier) and the type of nerve affected (motor, sensitive.). DIN are nowadays still fatal in some cases (e.g., 5-8% Guillain Barré Syndrome).

Dysimmune inflammatory peripheral neuropathies have become a major field of modern neurology, but the wide variety of causes and forms makes their diagnosis and their treatment still difficult. The lack of scientific and medical expertise of these rare disorders also explains diagnostic wandering of patients, which can last up to 16 years*.

DIAGRAM OF THE PERIPHERAL NERVOUS SYSTEM



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To confirm the diagnosis, the expertise of the neurologist is key

General practitioner (GP) is usually the first health care professional that suspects a neuropathy after an initial interview and physical examination of the patient. The ability of the GP to refer the patient to the right specialist is essential. The definitive diagnosis should be made by an expert (mostly a neurologist). Thus, a well-conducted neurological clinical examination associated to paraclinical examinations are usually sufficient to confirm the diagnosis.

** Neuroquali* (AFNP 2021)*

Importance of paraclinical examinations to support the diagnosis

Electroneuromyogram (ENMG) is an essential examination in exploring the peripheral nervous system. The aim of this technique is to measure the electrical activity, the speed and amplitude of nerve impulses and to assess nerves damages (axonal, demyelinating, conduction block…).

Lumbar puncture, and search for specific antibodies are also useful to identify the type of dysimmune inflammatory peripheral neuropathy. In the most difficult cases, nerve biopsy can be proposed.

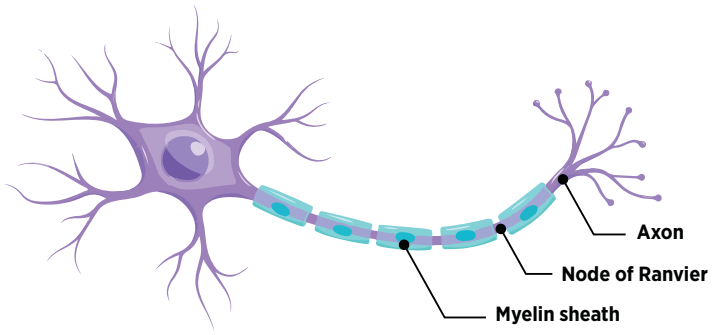
The major role of rare disease networks in Europe

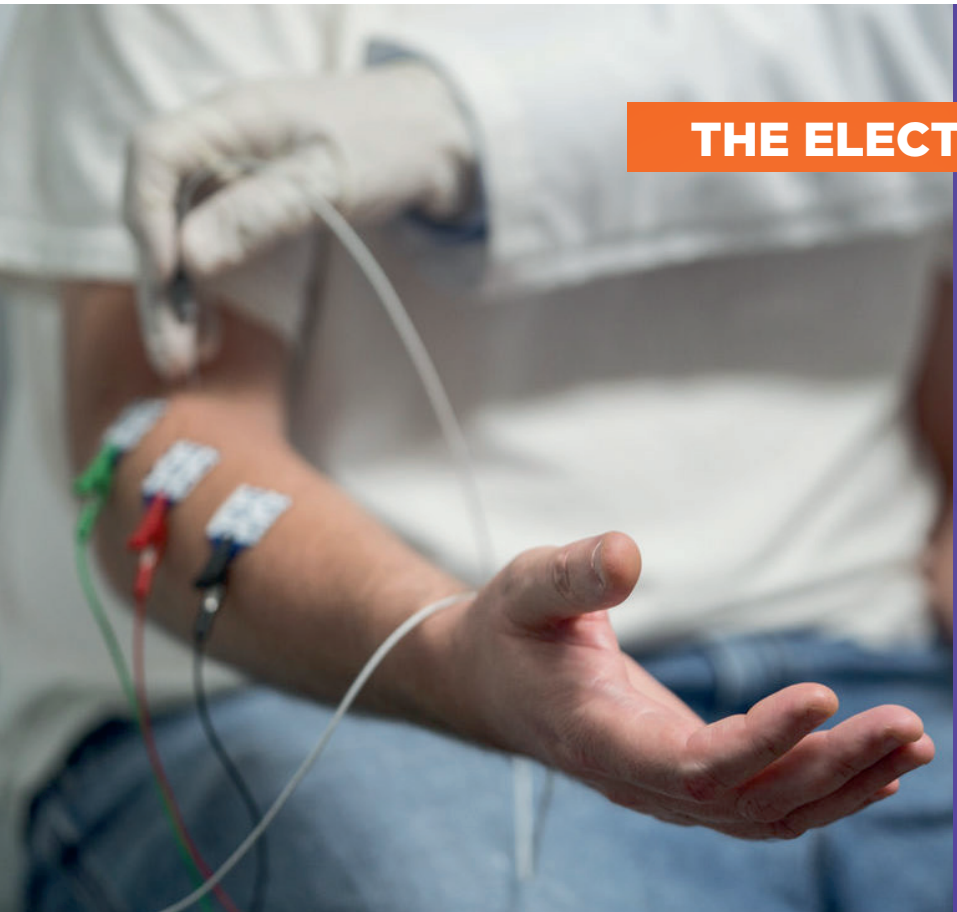
The small number of rare disease patients, their geographical dispersion and the low number of medical experts constitute obstacles to diagnosis and generally to access to care.

European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. They aim to facilitate discussion on complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources. They are under the authority of the European Commission.

The first ERNs were launched in March 2017 involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 EU countries. 24 ERNs are working on a range of thematic issues including bone disorders, childhood cancer, immunodeficiency and neuromuscular diseases.

DIAGRAM OF A NERVE WITH MYELIN SHEATH





THE ELECTRONEUROMYOGRAM

The Electroneuromyogram (ENMG) is a key examination in the diagnosis of dysimmune inflammatory peripheral neuropathies.
It records the electrical activity of a muscle or a nerve. The plot obtained during the recording is a graph corresponding to the electrical activity produced by the muscles or transmitted by the nerves.

Dysimmune Inflammatory neuropathies are part of the European Reference Network for Rare Neuromuscular Disease (EURO-NMD).

EURO-NMD

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

EURO-NMD (European Reference Network for Rare Neuromuscular Disease) brings together 61 health care institutions involved in neuromuscular diseases (50,000 affected patients in Europe) and spread over 14 Member States, as well as many very active patient organisations. EURO-NMD is based on three main pillars: care, education and research, while ensuring the implementation of best clinical and diagnostic practices, in order to improve the quality and equity of care in the Member States while fighting against diagnostic wandering.

A PUBLIC HEALTH CHALLENGE

2

ADAPTING THE HEALTH SYSTEM OF COUNTRIES AND EUROPEAN REGULATIONS TO REDUCE THE BURDEN OF THE DISEASE

- **Organisation of most healthcare systems in the world does not allow for an easy access to treatment which impacts the quality and continuity of care for patients living with dysimmune inflammatory peripheral neuropathies.**

Various immunotherapies have shown their interest to control the progress of the disease. Because of its safety profile, the first line therapy used today for DIN is intravenous immunoglobulins* (and more recently in several forms of chronic DIN subcutaneous immunoglobulins). Corticosteroids and plasma exchange (PE) are also useful treatments in the management of DIN.

As a second-line treatment, immunosuppressive therapies are sometimes proposed, even though their efficacy has not really been demonstrated.

PLASMA BAGS

- **Almost 580 plasma donations are needed to treat a patient* living with dysimmune inflammatory peripheral neuropathy for one year.**

70% of the plasma in the world is coming from the USA, which means that Europe and the rest of the world are massively dependent on the United States to cover the needs of patients. Increasing plasma collection worldwide has become a priority to ensure better quality and continuity of care for patients living with DIN but also for many other diseases such as haemophilia or primary immunodeficiency. In this respect, the revision of the European directive for the EU area may bring new perspectives for collections, compatible with the cultural and ethical aspects of all member states.

"The whole world depends on US plasma. The challenges of improving plasma collection are therefore essential for patients. The revision of the European Blood Directive, for example, is eagerly awaited by patients who depend on plasma-derived medical products said Jean-Philippe Plançon president of EPODIN. The issues of European self-sufficiency are at the core of the discussions, and we need all public and private plasma collectors to meet the needs of patients".

PLASMA DONATION: AN ACT OF SOLIDARITY

* *Polyvalent immunoglobulins are therapeutic proteins derived from human plasma. They are a major treatment for many dysimmune inflammatory peripheral neuropathies. However, the health crisis has led to a drop in blood and plasma donations worldwide, accentuating the risk of shortages of plasma-derived-medicinal products, particularly immunoglobulins, and leading many prescribing physicians to propose suboptimal therapeutic options for patients.*

European countries example

In many European countries, where health systems are still fragile, the situation is sometimes dramatic: in Romania, for example, only 2% of patients suffering from dysimmune inflammatory peripheral neuropathy are treated. Even in countries with robust health care systems, immunoglobulin shortages are common and long lasting. In Spain and Italy access is constantly disrupted and very unequal from one region to another. Changes of specialties, spacing infusions or stopping treatments, patients suffer every day from problems accessing prescription drug monitoring programs (PDMPs) which can be the cause of irreversible worsening of patients' health.

UNDERSTANDING THE PLASMA DONATION ECOSYSTEM

ITALY


FRANCE

UNITED STATES

The recommendation of the European Directorate for the Quality of Medicines (EDQM) is 33 plasma donations per year. Regarding plasma donation within the European union, very different collection systems coexist. Some countries, such as France (24 donation a year max.), have chosen to rely on a single public collector with very low compensation for donations (7€ max. provided that a request is made to the national collector), while others, such as Germany, authorise up to 60 donations per year and have opted for a mixed private-public system with compensation. Other countries, such as Austria, Hungary and Czech Republic, have allowed plasma collection centres run by pharmaceutical companies to be set up also with compensation for donors (around 25-30€). These countries are major suppliers of plasma in Europe.

In the USA, the Food and Drug Administration (FDA) authorises a donor to give plasma 104 times a year, mostly in return for remuneration.

3

REDUCE THE BURDEN OF DIN AND INEQUALITIES FOR PATIENTS

The absence of a diagnosis is always very difficult for patients and sometimes it can take years before identifying the disease.

The announcement of the diagnosis is also a singular moment in the patient's journey. The complexity of this medical area makes things even more difficult to understand for the patient and his entourage who cannot relate to already known diseases. Moreover, the sometimes-invisible nature of neuropathy, adds to the burden of patients who are already weakened, sometimes forcing them to justify their invisible symptoms.

This is why:

- Overall support for patients is essential, in particular by encouraging them to seek specialized support, to better cope with the disease, its pain, its physical and socio-professional impact. Adapt one's physical activity is also highly recommended to avoid chronic physical deconditioning and the acceleration of the loss of autonomy.
- It is important to make patients as independent as possible in dealing with their disease, particularly through therapeutic education. This is a major challenge because therapeutic education enables patients to limit their resort to healthcare and to lead a life consistent with the status of their disease (evolution, impact, typology).

4

DYSIMMUNE INFLAMMATORY PERIPHERAL NEUROPATHIES: UNKNOWN PATHOLOGIES, IGNORED SUFFERING

Rare, disabling and progressive diseases, dysimmune inflammatory peripheral neuropathies remain largely unknown to the general public, even though they affect nearly 1.3 million people worldwide. Their origin remains not well known, and fundamental research is under-resourced to meet the expectation of patients.

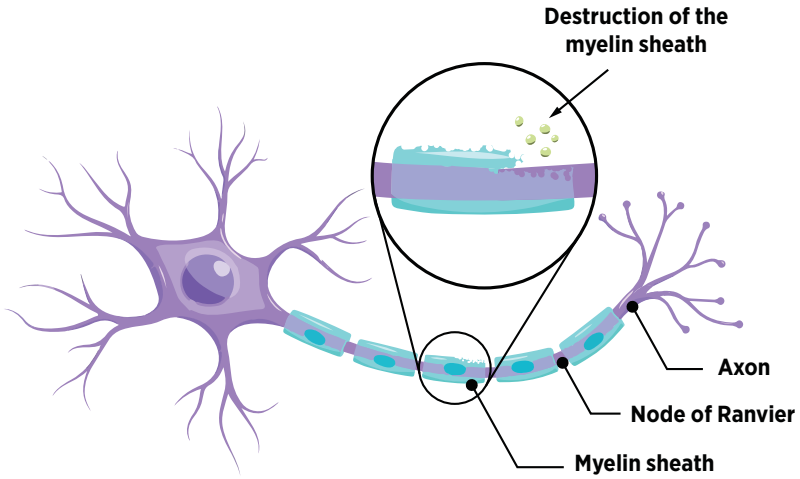
The mechanisms of the disease

The pathophysiological mechanisms of inflammatory neuropathies are presumed to be autoimmune in origin and are still largely unknown. The insulating myelin sheath that covers the axon and allows optimal conduction of nerve impulses is the target of an abnormal immune reaction involving lymphocytes (white blood cells) and macrophages (immune cells that contribute to the proper functioning of these tissues). Anatomical elements of the neuron such as the axon and nodes of Ranvier are also frequently affected. The result is a weakening of the capacity of the nerve fibre which, when repeated, can lead to major symptoms.

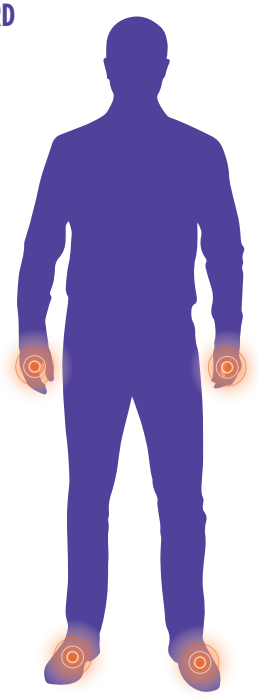
DIN ARE RARE DISEASES

Worldwide, it is estimated that 300 million people live with a rare disease, i.e., 4% to 5.9% of the world's population (Orphanet). Among these rare diseases, we find the dysimmune inflammatory peripheral neuropathies which affect about 1,3 million people in the world and cover a very broad spectrum. There are different forms of dysimmune inflammatory peripheral neuropathies: acute and chronic forms. Guillain-Barré syndrome is the best-known form of DIN. Some of them are very rare (e.g. Lewis-Sumner syndrome 1-4 / million people)

DIAGRAM OF A DAMAGED NERVE



THE TERM PERIPHERAL NEUROPATHY REFERS TO DAMAGE TO THE NERVES THAT CARRY INFORMATION TO THE BRAIN OR SPINAL CORD



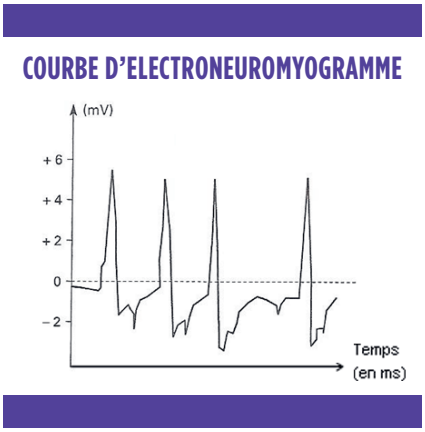
THERE IS A VERY LARGE NUMBER OF DYSIMMUNE INFLAMMATORY PERIPHERAL NEUROPATHIES THAT CAN INVOLVE ONE OR MORE NERVES:

- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)
- Lewis-Sumner Syndrome (LSS)
- Neuropathies associated with Monoclonal Gammopathies (GM including anti-MAG)
- Guillain-Barré Syndrome (GBS)
- Acute sensory-motor neuropathy (ASN)
- Acute motor axonal neuropathy (AMAN)
- Miller Fisher Syndrome (MFS)
- Immune-mediated small fibre neuropathies

5

DYSIMMUNE INFLAMMATORY PERIPHERAL NEUROPATHIES: MULTIPLE CAUSES, MULTIPLE FORMS, A HETEROGENEOUS FAMILY

Acute forms



- Guillain-Barré syndrome (GBS) or acute inflammatory polyneuropathy is one of the best known: It is a form of polyneuropathy that causes muscle weakness that usually worsens within days to weeks and then slowly returns to normal spontaneously. The exact causes of the disease are not known, but some favourable circumstances have been identified. Two thirds of patients have suffered from an infectious disease, most often of the respiratory system or gastroenteritis, in the days or weeks preceding the onset of the disease.

  Sometimes symptoms occur in the arms or head and progress downwards. There is rapidly worsening bilateral weakness of the lower limbs and then the upper limbs, often preceded or accompanied by paraesthesia (tingling, pins and needles, cold sensations). Cranial nerve involvement, particularly facial paralysis, is common. Clinical examination shows a limited absence of tendon reflexes at the beginning of the disease. Reflexes are diminished or absent. People with Guillain-Barré syndrome are immediately hospitalised, as the symptoms can rapidly worsen and in some cases lead to death.

  When the dysimmune reactions stop, regeneration and remyelination begin and lead to a rapid and almost complete regression of the paralysis. At one year, almost 70% of patients have recovered completely and 25% of patients remain disabled. GBS still kills in 5 to 8% of cases. Fatigue is a fundamental element to be taken into account, as about 80% of patients recovering from GBS will suffer from fatigue for a long time.

  Immunoglobulins (a plasma-derived solution containing many different antibodies collected from a group of donors), administered intravenously, or plasmapheresis (which involves filtering toxic substances, including antibodies to the myelin sheath, from the blood) accelerate recovery.

Chronic forms

- This category includes Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) whose dysimmune origin is very likely. Although in 80% of cases the motor deficit predominates, the demyelination process is random and multifocal, and asymmetries are observed. CIDP can present different forms: sensory, multifocal (sensory with central signs, with axonal forms, with monoclonal gammopathy)

- Lewis-Sumner syndrome (LSS) is a multifocal, sensory-motor demyelinating neuropathy of acquired dysimmune origin. It is about 5 times less common than common CIDP and accounts for about 1 to 4 cases per million population. LSS is often sensitive to intravenous and subcutaneous immunoglobulin (IgIG).

- Multifocal motor neuropathy (MMN). This is a dysimmune neuropathy characterised by a purely asymmetric, multifocal motor deficit, beginning and predominantly in the upper limbs, with a chronic course. Sensory

disorders are absent or minimal. Tendon reflexes are frequently abolished or diminished. Cranial nerves are exceptionally affected. Usually slow and progressive, MMN may sometimes progress in flare-ups followed by remission phases. Both LLS and MMN have multifocal involvement and the presence of persistent conduction blocks.

PATIENT TESTIMONIES

YANN STEPHAN

“My life was all mapped out and then suddenly the disease came along and turned everything upside down and gave me a double penalty.”

In the winter of 2010-2011, I experienced tingling and pins and needles in my lower limbs and, above all, immense fatigue and total exhaustion. In addition to this, there was a loss of sensitivity, hot and cold and burning sensations in the upper limbs.

At first, I didn’t pay attention to it but it didn’t stop, so I consulted my GP who immediately thought of a neurological dysfunction with my clinical picture. I was lucky because this doctor referred me to a neurologist and that’s when I began a long process of medical examinations: electroneuronogram, lumbar puncture, blood samples. In August 2011, 6 months after the first symptoms: I was diagnosed with chronic inflammatory demyelinating polyneuropathy. A few months before, I was 38 years old and in great shape. My life was all mapped out, and suddenly this illness turned everything upside down.

“Little by little, I have become an expert patient: over the last 10 years, I have accumulated 400 days of infusions and therefore have a capital of experience and valuable and indisputable everyday knowledge.”

Once the diagnosis was made, I had to understand the causes of the disease, with a large number of more or less invasive and tiring examinations, and while I was setting up my immunoglobulin treatments, as time went by, the cause did not impose itself, we were heading towards a dead end. So, I said to my neurologist: «Now we’ll deal with it...! And I started to accept the disease. Looking back, I realise how much the people who accompanied me at that time (including patient organization) helped me, supported me, guided me while respecting my own rhythm, and thus enabled me to accept the situation. This long-term dialogue prevented me from falling into isolation and depression. One cannot remain alone when the diagnosis is announced: at this stage, each patient should be accompanied by a patient-partner.

“One cannot be left alone when the diagnosis is announced: at this stage, each patient should be accompanied by a patient-partner.”

The long-term learning process of managing my illness, my experiential knowledge, added to the expertise of the doctors, has allowed a form of “Patient-Caregiver” co-construction to take place, where each one enriches

the other in their "practice". I have therefore gradually become an expert patient, a partner: over the last 10 years, I have accumulated 400 days of infusion and therefore have a capital of experience and valuable everyday knowledge.

The disease has reshuffled all the cards and today even if a lot remains to be done, I am happier than before my diagnosis because I am more accomplished. I have made this journey my strength

CHRISTINE LARRIEU

"I chose to self-administer my immunoglobulin treatment at home because it gives me back the power over my disease."

In 2019, I felt an intense exhaustion and a growing difficulty to move around. I consulted several health professionals, and this was the beginning of a 3-year diagnostic wandering. The symptoms got worse very quickly: I was staggering, I felt like I was walking on empty space. I was first diagnosed with severe anxiety and then suspected inner ear problems. Another false lead: as I have another chronic inflammatory disease, my gastroenterologist referred me to a rheumatology department for investigations, again without success. Fortunately, they then referred me to the neurology department of a reference centre for neuromuscular diseases. After an electromyogram, the diagnosis was finally made.

It took me 18 months to come to terms with it and to mourn: it takes time to accept it because your whole life is turned upside down. And it took a lot of trial and error to find the right immunoglobulin treatment. But now I am lucky enough to have found the right treatment that allows me to regain about 80% of my mobility. And I have chosen to administer my immunoglobulin treatment independently at home. In this way, I am regaining control over my illness. Today, I walk again at my own pace, albeit more slowly and in a safe environment, but I challenge myself physically and I take full advantage of these moments.

"It's amazing how much positive feedback you get from people when you accompany them. I find this active listening a source of great satisfaction, especially as it is different every time."