Good morning, ladies and gentlemen, and welcome to this series of conferences organized by St. Martin's Hospital on the occasion of the World **ALS** Day.

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During a series of meetings this week we will discuss various aspects linked with **ALS**. The meetings and workshops are addressed mainly to the patients' families, but also to doctors and to anyone who works in healthcare.

In my presentation today, which will serve as an introduction to the other meetings scheduled for today, I will try and give you a general framework of this disease, focusing on the causes, the **diagnosis** and the treatments currently available. I will also discuss the different directions research is taking at the moment. As I said before, I will not address my most expert colleagues, whom I'm very happy to see in the audience, but I will try to provide some basic information about this disease. Very often, unfortunately, the information people have is scarce or incomplete.

Let's start by defining **ALS**. **ALS** is a disease that affects **motor neurones**, i.e. the **nerve cells** of the brain and the **spinal cord** that are responsible for the movements of **voluntary muscles**.

ALS is the most frequent and most famous form of **motor neurone disease**. It causes a **progressive degeneration** of the **first motor neurone**, also called **central** or **cortical motor neurone**, and of the **second motor neurone**, also known as **peripheral motor neurone** or **spinal motor neurone**.

The specificity of **ALS** is that both the first and the second motor neurone degenerate and then die. The death of these cells happens gradually, over the course of several months or even years. The first signs of the disease appear when the number of **motor neurones** not working any longer is higher than the **motor neurones** that are still working. Over time, this leads to **progressive paralysis**. The name of this disease was chosen around the second half of the 19th-century by French **neurologist** Jean Martin Charcot. He used the term "lateral sclerosis" because **sclerosis** means hardening. In **ALS**, the lateral portion of the **spinal cord** - where the fibres of the **first motor neurone** are located - hardens. The term **amyotrophic** has to do with the loss of **muscle mass**, i.e. with **atrophy**. **Atrophy** is one of the most important **clinical signs** of this disease and is a consequence of the **degeneration** of the **second motor neuron**.

Now I will talk about the most relevant aspects when it comes to the **epidemiology** of this disease. **ALS** is considered a **rare disease**. The **incidence**, i.e. the number of new cases per year is around 2 to 3 cases in one year per 100,000 inhabitants. This holds true both for Italy and for the rest of Europe and America, however the incidence is quite homogenous all over the world.

The **prevalence**, which indicates the number of patients present in a community at a certain time, is instead equal to 4 to 10 cases per 100000 inhabitants. At present, there are around 5000 **ALS** patients in Italy. As I was saying at the beginning of my presentation, **ALS** is a disease we still know very little about. For example, people quite often wonder if it is a **hereditary disease.** Well, in most cases it is not. In 95% of cases, **ALS** is a **sporadic** disease. 5% of patients has however a **positive family**

history for this disease. This means that it is possible to find several cases of people affected by **ALS** in the same family.

Quite often we are faced with **autosomic dominant inheritance**. When there are more than one person affected in the family, we talk about **familial ALS**. Both familial forms of ALS and sporadic types of ALS present the same symptoms. We do not know the causes of ALS yet, but it is certain that ALS is not due to one single cause. It is due to several factors.

The numerous studies currently underway aim at determining the role of some elements, of some factors in order to establish if they can be considered **risk factors**.

For example an excess in **glutamate** can be a cause of **ALS**. **Glutamate** is an **amino acid** used by **nerve cells** as a **chemical signal**. It is believed to play an important role in **ALS**. Some studies have focused on various **toxic environmental factors** whose role has not been identified with certainty. Some examples are **cigarette smoke**, mechanical trauma which also includes physical activity and intense sport activity. It is not my chance that in America **ALS** is called **Lou Gerig's disease**. This name comes from a famous baseball player who died because of this disease. Other t**oxic environmental factors** that could potentially need to **ALS** are the exposure to toxic substances such as **pesticides**, **herbicides** and some **insecticides**, the exposure to **heavy metals**, for instance to **mercury**, **lead** and **arsenic**, and finally **genetic predisposition**. Over the past few years, research has focused on **genetic factors**, which are not only a cause of familial forms of **ALS**, but might also play an important role in **sporadic ALS**.

Gene mutations might be a cause of **ALS**. A **mutation** in the **superoxide-dysmutase gene**, also known as **SOD1 gene**, was discovered in 1993. Since then, the list of genes associated with **ALS** keeps growing, also thanks to new technology to study our DNA. About two-thirds of all cases of **familial ALS** are caused by mutations of four genes, among which the **SOD1 gene**.

Let's now talk about the symptoms of **amyotrophic lateral sclerosis**. This is the last topic I will focus on in the first part of my speech. **ALS** symptoms can be divided into symptoms due to **first motor neurone damage** and symptoms due to **second motor neurone damage**.

The main symptoms of **first motor neurone damage** are **spastic laughter and bouts of crying**, i.e. the inability to control laughter and crying, **dysarthria**, **dysphagia**, **strength deficit**, **spasticity**, an increase in **tendon reflexes** and in **pathological reflexes**. In the second case, the most evident symptoms are **tongue atrophy**, **hypophonia**, **muscle hypotonia**, **cramps** and **fasciculations**.

In most cases, **ALS** has a **spinal onset**, and starts as a **strength deficit** which affects the muscles **innervated** by the **motor neurone** of the **spinal cord**, such as the **upper limbs**, the lower limbs, the neck and the trunk. At the onset, the deficit is located in some specific areas, which is why it is defined as **focal onset**.

Very well, I think we can take a short break now. Let's meet in 10 minutes in this room for the second part of my speech.

SECOND PART

Ladies and gentlemen, welcome back! Thanks again for taking part in today's meeting. As a researcher, it is very gratifying to see how many people are aware of the importance of knowing a disease well, in order to be able to deal with it. Thanks to your interest and your support, research can keep taking steps forward.

You know, many ask me whether it is difficult to conduct research on a disease which is still incurable. I always answer that my colleagues and I work very hard and with a lot of enthusiasm especially because we know that a cure is an attainable goal, because we know that with our work we can really help a lot of people. I'm not one talking about patients, but also about their families.

I would like to take a few steps back now and talk in more detail about the onset. I will focus on the rarest cases, in which the disease has a **respiratory onset**. In these cases, coming up with a **diagnosis** of **ALS** is very difficult, because the first symptom is usually **weight loss**. **Weight loss** is not so easily associated with **respiratory failure**. If the disease manifested as a **dyspnoea**, things would be easier. Luckily, we can study a patient's **respiratory function** to understand whether the **weight loss** observed is due to **respiratory insufficiency** or not. As many of you probably know, **ALS** is a disease that affects the **motor system**, but does not affect all other functions. This is true in most cases, but there are also situations in which **ALS** is associated with **dementia**. In most cases, with f**ronto-temporal dementia**. This type of **dementia** can cause **behavioural changes** and can even lead to **aggressiveness**. This of course represents a serious issues for caregivers, because they also have to deal with the cognitive side as well.

Let's now move on to the next aspect I would like to give you some information about: the **diagnosis**. Is there a **diagnostic test** that allows us to identify **ALS** with absolute certainty? It is difficult to formulate a **diagnosis** of **ALS**, because it requires various medical tests and a clinical evaluation repeated over time by an expert **neurologist**.

There isn't a specific exam that allows us to establish with absolute certainty that a person is affected by **ALS**. There are, however, a series of analyses than can be made, as I was saying. Let's start with the initial tests. First of all, doctors perform an **electromyography**, i.e. an exam that aims at finding **signs of suffering of the second motor neurone** in the arm and leg muscles. Then, **liver exams** and an **MRI** are carried out, to exclude other potential causes. Even though an **MRI** performed on an **ALS** patient may not show anything abnormal, it can still help us check whether the symptoms can be explained by lesions in the brain or in the spinal cord. In some cases, it might be necessary to perform a **lumbar puncture** to examine the **cerebrospinal fluid**. In other cases, a muscle and a **nerve biopsy** can be helpful. After the initial diagnosis, further exams are performed to confirm the diagnosis.

Therefore, another **electromyography** is performed, and then also a **spirometry**, which is used to assess the efficiency of the **respiratory muscles**. Later on, a **blood gas analysis** is conducted. With this exam, the amount of oxygen and carbon dioxide present in the **arterial blood** is measured. Other

exams can be performed with the aim of ruling out other potential cause for the symptoms, such as a **CT-scan**.

There are, in fact, several diseases that can look like **ALS**, but aren't. I'm going to name a few: **multifocal motor neuropathy**, **Kennedy's disease**, **bulbospinal muscular atrophy**, s**pastic paraparesis**, **HIV**, **cervical spondylotic myelopathy**.

When a patient has **respiratory failure**, which is the actual cause of death in the final stage of the disease, the only solution is, unfortunately, **invasive ventilation**. The goal of therapy isn't however only slowing down the **progression** of the disease itself, but also improving the quality of life of the patient.

Over the past few years, research has increased and the hope of finding a cure soon is becoming more and more a reality. But in the meantime, having sufficient information, and detailed information, can really help patients and also their families and caregivers. That is why we are here today and this is what we are trying to achieve with this series of conferences. I conclude my presentation here and wish you a nice and informative day. Of course, I also encourage you to take part in the meetings and workshops organised for today and the next few days. Thanks for listening!