Ladies and gentlemen, I am very honoured for this invitation and I am very happy to speak on this very important occasion, on this day dedicated to improving our professional knowledge. So thanks again very much to the organisers and the sponsors for making this event possible. Thanks and welcome to all participants. I know that today's audience is quite varied, there are experts, patients, family members. I know that you know ALS very well, but I think it is important to start from the basics before going into more detail about some aspects I dealt with in the last few years as a researchers at the ALS research centre at St. Martin's hospital.

This disease is a very complex one. We cannot deny it.

The first element of complexity is the name itself. **ALS** stays for "**amyotrophic lateral sclerosis**". The name is quite obscure and I guess most people don't know what it means. It was the founder of modern neurology, Dr. Charcot, who defined this disease as "**amyotrophic lateral sclerosis**". Why did he choose this name? Well because the **lateral portion of the spinal cord** of the people affected by this disease is hardened, so we say that ALS patients present a **sclerosis** of the **lateral spinal cord**. The third element of the name, **amyotrophic**, means that there is a loss of **muscles mass**, a lack of muscle, we could say. Doctors call this phenomenon **muscle hypotonia**.

This disease is also called **motor neurone disease** because it affects the main cells of the **motor system**. ALS causes a **degeneration** of **motor neurones**, the **nerve** cells responsible for the movement of **voluntary** muscles. Motor **neurones** are divided into two groups: there's the **first motor neurone** or **central motor neurone**. it is also known as **cortical motor neurone**. Then we have the **second motor neurone** also called **peripheral motor neurone or spinal motor neurone.** The first **motor neurone** sends impulses to the **spinal cord**, while the **second motor neurone** sends messages directly to the muscles. This classification, this distinction between the **first** and the **second motor neurone** is very important because scientists classify the diseases that are part of the big family of **motor neurone diseases** on the basis of this difference.

The main consequence of this disease is a **progressive paralysis** that affects the **limbs**, but patients also lose the ability to speak, presenting **hypophonia**, to swallow and in the final phase of the disease, unfortunately, also the ability to breathe.

These are however only some of the symptoms. When the secondary motor neurone dies, this progressively leads to **atrophy**. Atrophy is, however, a sign that develops in the later stages of the disease. Why? Well, it takes time for the muscle to shrink, it takes months, it is not a quick process. So atrophy goes hand in hand with weakness.

Other symptoms of **ALS**, apart from atrophy, are **fasciculations**, that is very short and spontaneous **muscle contractions** that are therefore involuntary. But there are also other symptoms such as **cramps**, **spasticity, pathological reflexes** and an increase in **tendon reflexes.** ALS patients generally also present **dysarthria**, that is the difficulty in articulating words, a difficulty in speaking and communicating. Another symptom is **dysphagia**, that is a difficulty in swallowing. This can be a very serious problem because the patient can suffocate due to **dysphagia**. Both of these conditions can be a

consequence of **tongue atrophy**. There is another very specific symptom, which is **uncontrollable laughter** and **bouts of crying**. What do these words mean? It means that the patient is no longer able to control laughing and crying. These manifestations, which normally express how the person is feeling, such as sadness or happiness, actually have nothing to do with the patients' emotions, because they're neither sad nor happy. Just imagine how difficult it is for those who take care of the patients to understand their needs and how this situation can be embarrassing for patients, because they are affected in their body but are still mentally present.

Another symptom which is sometimes associated with ALS is dementia. 15% of patients can present **dementia** at onset or develop it during the course of the disease. We are usually faced with **fronto-temporal dementia**. This leads to **behaviour changes**, mood swings and **aggressiveness**. In other cases, patients do not develop dementia.

From a clinical point of view, **ALS** can present different types of **onset.** In most cases, ALS has a **spinal onset** and manifests as a **strength deficit** which involves the muscles **innervated** by motor neurons of the spinal cord, for example the muscles of the **upper limbs**. At the beginning, the deficit is localised in specific areas. That's why we talk about **focal onset**.

There is a very rare form of ALS that has a **respiratory onset**. It is a very problematic form of ALS, first of all because it is difficult to recognise it. It doesn't manifest through **dyspnoea**, that is through a loss in **respiratory function**, but rather through **weight loss** which is usually considered to be cause by other factors, for example to metabolism. It is therefore important to be able to analyse the **respiratory function** of a patient who is losing weight, because weight loss could be due to **respiratory failure**. If these forms are not recognised in time, patients can reach a stage where they need **invasive ventilation**, even quite soon after onset. So an early diagnosis allows us to support a patient's respiratory function in a non-invasive way. This way we can fight or at least delay the need for invasive ventilation.

So how do we identify ALS? The diagnostic process is based on the identification of **signs of suffering of the first and the second motor neuron**. There must be some **clinical signs** that the motor neurones have been compromised. These signs must present a **progression**, which means that they have to get worse and advance over time, so that within 6 to 12 months from the onset other districts are affected too. To identify these elements, an **electromyography** can be very useful. The **electromyography** is an examination of the muscle that is conducted with the help of a needle and it helps us make sure that lower motor neurons work correctly.

We must then also try and rule out other diseases which might present similar symptoms to amyotrophic lateral sclerosis, because some of these diseases can be cured. Let's not forget that ALS is an incurable disease, at least today. How can we verify that we are not faced with other disease? We can do this for example through an **MRI**, as I explained earlier, or with the help of a **muscle biopsy** and other laboratory tests which have the same goal. What we don't have as of yet is a **diagnostic test.** More rarely we might need to perform a **lumbar puncture** to examine the **cerebrospinal fluid**. After

the initial diagnosis other **diagnostic exams** are carried out to confirm the **diagnosis**. A **spirometry** can be carried out to verify whether the **respiratory muscles** are still working properly. In addition to this exam, a **blood gas analysis** that checks the amount of carbon dioxide and oxygen in the **arterial blood** can be very useful to rule out other diseases. If doctors suspect the symptoms might be due to other diseases, they may also decide to perform **liver exams** or even a **CT-scan**. As you can see, it is not easy to correctly diagnose ALS. Several other conditions can have similar symptoms to ALS, for example **spastic paraparesis**, **cervical spondylotic myelopathy**, **Kennedy's disease**, **bulbospinal muscular atrophy** and **multifocal motor neuropathy.** An expert **neurologist** will know what to look for. It is important that these tests are repeated over time to make sure we can rule out diseases that present similar symptoms.

Let's take a short break now. We will start again in 15 minutes with the second part of my presentation.

SECOND PART

Welcome back and thanks again for being here today. I know you are getting a lot of information and you might already know some of the things we're discussing today, but I hope every one of you will discover something new about this disease. Conducting research on this disease is constant challenge for researchers, and there are many different aspects of the disease we are focusing on. Some of us try to develop a way to diagnose ALS more easily, but a lot of research has been done on another aspect that is equally interesting and could help us find an effective cure or at least work on prevention, namely on the causes of ALS. There are many theories about the causes, which have helped identify some of the **risk factors** for ALS.

Among the many hypotheses, the most famous one, which most of you will probably have heard of, is the one linked with physical activity. In Italy, for example, there's been a lot of talk about ALS as the "football players' disease". As far as football is concerned, an increase in the **prevalence** of this disease has been explained through various hypotheses. Researchers are mainly focusing on physical activity and repeated trauma as potential causes. This **correlation** between sports and **ALS** became very famous in America too, where **ALS** is also very famous as **Lou Gehrig's disease**, from the name of a famous baseball player who died of this disease in the 30s.

There is a very interesting and quite recent line of research which is investigating the potential correlation between amyotrophic lateral sclerosis and certain eating habits. Some studies have shown that there is a correlation between the **incidence** of ALS and the levels of **glutamate** in the diet. These studies have shown that the incidence of the disease is higher in the populations where there is a higher consumption of glutamate. This ingredient is usually used to make food more savoury. Glutamate is an **amino acid** used by **nerve cells** as a chemical signal. When the amount of glutamate is too elevated, it cause a hyperactivity of nerve cells which can be harmful. This mechanism seems to play an important role in ALS.

Another line fo research is focusing on **toxic environmental factors**. For instance, **cigarette smoke** seems to be a risk factor, especially for women. The exposure to pesticides and insecticides might also represent a risk factor. The same can be said for the exposure to heavy metals such as **lead, mercury** and **arsenic**.

I will now move on to another very fascinating topic, namely that of **genetic factors**. The presence of forms of **familial ALS**, i.e. of cases in which the patients present a **positive familial history** of ALS, has lead researchers to analyse the patients history more thoroughly.

While in **hereditary diseases** there is just one gene or a few genes responsible for them, when it comes to complex diseases such as ALS there is probably a group of genes that cause the disease when combined. This happens rarely, I mean it is rare that all these genes that cause the disease present some kind of alteration at the same time. In fact, most of these diseases are still **rare** diseases, as **epidemiology** tells us. Thanks to research, we have managed to identify around 15 genes that are involved for sure not only in **hereditary ALS**, but also in **sporadic ALS**. When talking about **hereditary ALS**, we are mainly faced with **autosomic dominant inheritance**.

In 1993 the first gene associated with ALS was identified. I'm talking about the gene which codifies **superoxide-dysmutase**, which is commonly called **SOD1**. Some families were analysed in detail and following studies showed that 20% of familial forms, which is a rather small percentage, show a mutation of the **SOD1 gene**. In the following years, researchers found out that if we take into consideration sporadic patients, 2% of them also present a SOD mutation. This element certainly encouraged research to identify other potential genetic alterations that can justify or at least cause **genetic predisposition** to the disease.

Now I don't want to get more into detail about this because I don't want to bore you and I know that these medical aspects are quite complex to understand, but I hope I have managed to give you some additional information on this disease and I am available for any questions or comments. Thank you for your attention.