This booklet has been written with the intention of providing full and up-to-date information on Aicardi-Goutières syndrome.

The information it contains is scientifically accurate and presented in a concise and understandable way so that it might be useful for general practitioners and family paediatricians, for the families of affected children, and for all those who, for different reasons, have first-hand experience of this disease.

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GLOSSARY
Aicardi-Goutières Syndrome (AGS) is a rare autosomal recessive encephalopathy with onset in the first year of life, characterised by microcephaly, severe psychomotor delay, and spasticity with signs of extrapyramidal involvement.

The International Aicardi-Goutières Syndrome Association (IAGSA) was founded in June 2000 as a no-profit organisation whose aim is to coordinate the efforts of parents, doctors and therapists in order to raise awareness and spread knowledge of Aicardi-Goutières syndrome (AGS).

**PURPOSES**

- to provide updated information;
- to offer consultation;
- to promote collaborations through contacts with doctors and health organisations internationally;
- to promote and support scientific research in areas linked with AGS.

The diagnosis is based on clinical signs, on a neuroradiological picture of cerebral calcifications, white matter abnormalities and cerebral atrophy, and on CSF chronic lymphocytosis and raised levels of interferon-alpha, in the absence of demonstrable pre-/perinatal infections.

Genetic studies have led to the identification of at least four genes that, if mutated, can give rise to AGS. It is likely that further genes will be identified.

Genetic studies have led to the identification of at least four genes that, if mutated, can give rise to AGS.

Sample collected by IAGSA (total of 68 patients)

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IAGSA

IAGSA (International Aicardi-Goutières Syndrome Association) is the first international association devoted to Aicardi-Goutières syndrome (AGS). It was founded in 2000 by the families of children affected by AGS and Prof. J. Aicardi is its Honorary President.

IAGSA organised the first two international meetings on AGS, one in 2001 and the other in 2006; held in Pavia, both events saw the active participation of physicians and families of affected children from all over the world. IAGSA, over the years, has also promoted research into the disease, primarily supporting contact and collaboration between major international experts in the different related areas (Prof. Y. Crow, Prof. P. Lebon, Prof. T.W. Kuijpers).

IAGSA works to raise the level of awareness and knowledge of AGS, and has created and funded a website. The association has also funded various research and scientific collaboration projects between centres both within and outside Italy (Prof. Y. Crow, Manchester; Prof. A. Izzotti, Genoa).

Over the years, IAGSA has collected data from many AGS patients (currently 68). Of these, 28 have been seen directly by IAGSA child neurologists, who have acquired considerable and unique clinical experience in this field and published some important scientific papers on the clinical aspects and natural history of the disease.

The IAGSA child neurologists are affiliated with and able to use the facilities and diagnostic resources of the Department of Child Neurology and Psychiatry at the IRCCS “C. Mondino Institute of Neurology” Foundation, in Pavia, Italy. The C. Mondino Foundation is also the registered headquarters of the association.
Contact with families (including the organisation of meetings with and between families), with research centres in Italy and abroad and with various sporting associations is coordinated by the association’s operational headquarters (Via Vittadini, 1 - 27100 Pavia, Italy). The operational headquarters is also involved in procuring the funds essential for the ongoing scientific research and various other initiatives.

Central to the activity of the association is the work carried out by the representatives of the families of affected children. The families’ representatives, with great empathy and drawing on their own experience, follow closely the many problems that, every day, confront the parents of affected children who turn to them for their help. With their support, these parents find the strength to cope with the evolution of their children’s disease. With the help and support of the families’ representatives, IAGSA organised, free of charge, two short holidays in Alassio (at the Casa al Mare AGOAL) for a group of Italian families with children affected by AGS. These holidays, one in 2005 and the other in 2006, gave the families an opportunity to “compare notes” on the various and difficult problems that they encounter on a daily basis and also to meet doctors and researchers who work for the association.

IAGSA, as a registered member of the Italian Rare Diseases Federation and the European Organisation for Rare Diseases (Eurordis), supports and takes part in “Uniamo - Federazione Italiana Malattie Rare” and Eurordis initiatives. In 2005, the association submitted a project “Genomica e proteomica della sindrome di Aicardi-Goutièrè” (“Genomics and proteomics in AGS”) to the Fondazione Cariplo and was awarded funding by this organisation. In 2008, in collaboration with Prof. P. Lebon (Paris), a study was started focusing on the problem of vaccinations in children with AGS. These are some of the many projects carried forward by IAGSA, which, with the intention and hope of offering some help to the children and families so sorely tested by this disease, pours its efforts into scientific research into Aicardi-Goutièrè syndrome.
What Aicardi-Goutières syndrome is

Aicardi-Goutières syndrome (AGS) is a rare genetic disorder with an autosomal recessive pattern of inheritance. The main clinical features of AGS are microcephaly, neurological signs of pyramidal tract and extrapyramidal pathway involvement, cerebral (basal ganglia) calcifications, leukodystrophy and cerebral atrophy; other characteristic findings are chronic lymphocytosis and raised levels of interferon-alpha (INF-alpha) in the cerebrospinal fluid (CSF).

Who discovered it

In 1984, Jean Aicardi and Françoise Goutières described eight children, from five different families, showing a severe and progressive early-onset encephalopathy characterised by the presence of basal ganglia calcifications, white matter abnormalities and chronic lymphocytosis in the CSF.

The recurrence of this picture in siblings whose parents were consanguineous, together with the finding that both males and females could be affected, immediately suggested that this was a disease inherited as an autosomal recessive trait and at the same time highlighted the risk, from a clinical point of view, of mistaking this picture for the sequelae of congenital infection. Aicardi drew attention to cases previously described in the literature that may be the same clinical entity. A few years later, Lebon identified a further typical feature, helping to establish a more accurate diagnostic profile of the syndrome: the presence of raised levels of INF-alpha in the CSF in the absence of demonstrable infections of the brain.

The eponym “Aicardi-Goutières syndrome” was used for the first time in 1992, and the years that followed saw a rapid increase in the number of new cases identified. By 2001, the year of the first International Meeting on AGS, organised by IAGSA in Pavia, Italy, the number of known cases had risen to around 50, originating mainly from Europe and America, and there was a growing
realisation that there probably existed many more cases, as yet unrecognised.

To date, thanks above all to the recent identification of different genes that, if mutated, give rise to the syndrome, and also to the emergence of a broader and more heterogeneous clinical spectrum of AGS, over 100 cases have been reported and the disease has started to show a wider geographical distribution (there are now descriptions of cases in Africa and Asia, too).

How it manifests itself

AGS typically has onset in the first year of life, usually at the age of around four months. It follows an uncomplicated pregnancy and delivery and apparently normal early development. Extreme irritability, disturbed sleep-wake patterns (including difficulty falling asleep) and feeding difficulties are frequent early alarm signals. Low-grade fevers (38-38.5°C), sometimes recurrent and not apparently linked to any infection, are commonly reported at clinical onset. The presence of these symptoms can initially lead to erroneous diagnoses of meningitis or encephalitis, but what they actually indicate is the onset of an initially sub-acute encephalopathy. In this picture, there emerges an increasingly apparent psychomotor delay and/or a loss of early acquired skills, as well as signs of neurological impairment and a slowing of head growth.

After this first phase, which usually lasts a few months, the clinical picture typically stabilises and, according to most authors, no further progression of the disease is detectable.

The stimulus triggering the onset of the disease is not known, and neither is it understood why, after several months, the clinical picture stabilises.

In about 20% of patients, the disease instead manifests itself in the neonatal period. In these cases, the picture - neonatal neurological impairment, microcephaly (sometimes severe) and
calcifications (these two features sometimes detected in utero),
transitory hepatosplenomegaly with raised transaminases, reduction
of platelets and anaemia - is even more difficult to distinguish
from those of congenital viral infections.

There have recently been reports of cases with an atypical
age at onset (i.e. over 12 months of age), in whom the disease
appears after a more prolonged period of normal psychomotor
development.

**Neurological signs**

During or immediately after the onset phase, the neurological
signs typical of AGS progressively appear.

Affected subjects generally develop tetraplegia, poor head
control, trunk hypotonia, pyramidal and extrapyramidal signs, in
particular persistence of archaic reflexes, and dystonic postures
and movements, sometimes associated with varying degrees of
rigidity.

They also frequently present abnormal eye movements,
nystagmus and poor visual performance. Another typical finding
in affected subjects is the presence of the “startle reaction” in
response to even mild sensory stimuli.

The reported frequency of epilepsy in AGS ranges from 25% of
cases, reported by some authors, to 53% in the more recent
literature.

The vast majority of affected subjects present severe motor
and cognitive impairment: postural acquisitions are frequently
limited to partial head control and language is severely impaired,
indeed absent in most cases, even though some subjects show
some awareness of their surroundings and a degree of
understanding.

As regards the severity of the clinical picture, there exists a
certain heterogeneity, even within the same family.
Extraneurological signs

Extraneurological signs are frequent in AGS. The organ most typically affected is the skin, which can present chilblain-like lesions characterised by areas of inflammation and intermittent necrosis. These lesions, reported in around 40% of subjects at least once in their lifetime, are found mainly on the fingers, toes and ears. Although more usual in winter, they can sometimes be present throughout the year.

There are also other extraneurological symptoms, reported less frequently in sporadic cases of AGS: as well as liver involvement (hepatosplenomegaly and raised transaminases), patients can also present transitory reduction of platelets, both these problems being found above all in cases with neonatal onset.

There have also been reports of congenital glaucoma, raised levels of autoantibodies, hypothyroidism, insulin-dependent diabetes mellitus, haemolytic anaemia, polygammaglobulinaemia, neonatal cardiomyopathy, demyelinating peripheral neuropathy, micropenis, and transitory antidiuretic hormone deficiency.
AICARDI-GOUTIÈRES SYNDROME

Neuroimaging findings

There are three cardinal neuroradiological features of AGS: cerebral calcifications, white matter abnormalities, and cerebral atrophy. The calcifications, typically bilateral and located in the basal ganglia, particularly the globus pallidus, putamen, caudate nucleus and often the cerebellar dentate nuclei, are best visualised on CT scan. Often, the calcifications extend to the white matter; they may be punctuate or larger and more confluent. Nearly always present at diagnosis of AGS, the calcifications tend to remain stable over time, even though they have shown a progression in a few cases. It is very important to be aware that in the presence of a clinical picture suggestive of AGS, the cerebral calcifications constitute a very important diagnostic sign; since they are not easily identified on MRI, they should be carefully sought on CT scans in all cases of unexplained leukoencephalopathy. It is also important to remember that these calcifications need not necessarily be present from the onset of the disease, but can appear subsequently, as reported in some cases.

Therefore, at onset at least, the presence of cerebral calcifications should not be regarded as indispensable for a diagnosis of AGS.

Horizontal section of the brain at the level of the basal ganglia.
The illustration on the left shows the anatomical structures involved in AGS, while the CT image on the right shows the corresponding lesions.
Another typical feature of the syndrome is the presence of white matter abnormalities, often showing a clearly leukodystrophic pattern.

Found in 75-100% of cases, these abnormalities are detectable as hypodense areas on CT scans or, more clearly, as a hyperintense signal on T2-weighted brain MRI.

These abnormalities seem to be located mainly in the frontal and temporal lobar areas, sometimes showing a tendency to cystic degeneration.

Cerebral atrophy is the third cardinal neuroradiological feature of AGS, present in 94% of the cases reported in the literature.

It remains stable or tends to progress in cases followed up over time.

**Cerebrospinal fluid**

Analysis of the CSF is an important part of the diagnostic workup in AGS as it can reveal specific abnormalities, in particular CSF lymphocytosis (>5-100 cells/mm³) and raised levels of INF-alpha (>2 UI/ml); raised levels of INF-alpha can also be found in the blood plasma, but, being less marked and less constant than the INF-alpha increases found in the CSF, they do not have the same diagnostic value.

Both the lymphocytosis and the increased INF-alpha concentrations in the CSF are very marked at the onset of the disease, and thus in the course of the first year of life, after which, over time, they tend to regress gradually to reach normal levels between the ages of 3 and 4 years.

In 2003, alterations in CSF metabolites were described in patients with AGS, particularly in pterins (found to be increased) and folates (reduced). This pattern may represent another CSF marker of AGS and could be a consequence of the overproduction of IFN-alpha in the disease.
Genetics

From as early as the first clinical description of the disease, it was suspected that AGS had a genetic aetiology. With the identification of the first locus on chromosome 3, an autosomal recessive mode of transmission was soon established. It also quickly became clear that AGS is genetically heterogeneous, meaning that mutations in different genes can produce the phenotype typical of the syndrome. The second locus was identified on chromosome 13 in 2006.

This was followed shortly afterwards by the identification of the 4 genes associated with the syndrome (and of the mutations in them): these are TREX1, on chromosome 3, known as AGS1; RNaseH2B on chromosome 13, known as AGS2; RNaseH2C on chromosome 11, known as AGS3; and RNaseH2A on chromosome 19, known as AGS4.

TREX1 codes for an enzyme (DNase III) involved in breaking down single-strand DNA; the RNaseH2A, B and C genes encode three separate proteins that function as a single enzyme complex called RNaseH2 which, instead, is involved in breaking down RNA. There are reports of rare cases of AGS with heterozygous TREX1 mutations; this indicates that there may exist rare forms of
AGS associated with a de novo mutation (i.e. not transmitted by the parents but present only in the foetus) and an autosomal dominant pattern of inheritance.

Mutations in these four genes have been found in 83% of patients, in whom the diagnosis of AGS is thus confirmed; this means that there must exist other genes, still to be identified, responsible for the disease in the remaining 17% of cases.

Recently, a fifth AGS-causing gene has been identified (AGS5), although its function has not yet been established (unpublished data).

Looking at affected families, the frequency of mutations in the four known genes has been found to differ: mutations in the RNaseH2B (AGS2) gene, found in 40% of AGS patients known to have a mutation, are the most frequent, followed by mutations in TREX1 (AGS1) (25%), which is the gene most frequently mutated in Northern European families.

Mutations in the RNaseH2C (AGS3) gene are more rare (14%) and found almost exclusively in families from Pakistan. Finally, mutations in RNaseH2A (AGS4) are the rarest, found in 4% of all patients with mutations.

Some genotype-phenotype correlations have been reported: in particular, the forms characterised by very early onset (in the neonatal period), a more severe clinical picture, and a higher childhood mortality rate (around 34%) are associated with mutations in the TREX1, RNaseH2A and RNaseH2C genes, whereas the later-onset forms (i.e. onset after the first months of life), in which the clinical picture is still severe but life expectancy is longer, are - like the atypical pictures in which intellectual function is relatively preserved - more frequently associated with mutations in the RNaseH2B gene.
AGS5: SAMHD1 PROTEIN

In 2009 a fifth AGS gene (AGS5), SAMHD1, coding for a protein of unknown function but exhibiting a domain usually involved in binding RNA, was identified on chromosome 20 (Chr 20q11).

The function of the SAMHD1 gene product has not yet been established. The protein is probably implicated in immune function, given that it is upregulated in response to viral infections, and it could have a protective role in preventing self-activation of innate immunity. From clinical point of view, it seems that some patients with mutations in AGS5 SAMHD1 are at risk of developing a form of cerebral vasculopathy that has never been described in patients with mutations in AGS1 to AGS4.

This vasculopathy is characterised by the presence of intracerebral large artery disease with a picture of extensive stenoses (narrowing) of intracerebral large arteries, Moya Moya disease, intracranial aneurysms and arterial thrombosis. These findings have been interpreted as related to a particular role for the SAMHD1 protein in blood vessel integrity and homeostasis.

It is therefore very important, given the potential for intervention, that subjects with mutations in SAMHD1 be actively screened for intracranial arteriopathy. Furthermore it has also been proposed that arthropathy with progressive contractures should be considered part of the spectrum of Aicardi-Goutières syndrome due to SAMHD1 mutations.
Pathogenesis

The identification of the genes responsible for AGS, together with the available clinical and experimental evidence, provide clues that may help to clarify the pathogenesis of the syndrome. Indeed, even though the enzymatic function of the TREX1 protein and the RNaseH2 complex is not fully understood, there seems to be no doubt that both are involved in the process of removing nucleic acid fragments produced as a result of normal cell cycles. When they do not function properly, because of a genetic mutation, fragments of nucleic acids (DNA and RNA) will build up and could activate the innate immune system (the idea is that the organism mistakes them for DNA and RNA of viral origin). Activation of the autoimmune system may trigger an inappropriate release of INF-alpha, which is probably responsible for the clinical picture of the syndrome. This hypothesis would also explain why AGS has a clinical picture similar to those of congenital infections and of some autoimmune disorders, particularly systemic lupus erythematosus, which affect different organs and systems as shown in the figure below.

Hypothesis that Aicardi-Goutières syndrome is due to a mutation in the TREX1, RNaseH2B, RNaseH2C and RNaseH2A genes.
It has long been hypothesised that INF-alpha is involved in the pathogenesis of AGS: the vascular changes and calcifications seen in AGS are very similar to those reported in the transgenic mouse model of INF-alpha overproduction (the animal model of AGS).

The clinical evolution of AGS, together with the CSF data, also suggests that an initial “active” stage of the disease, in which the level of INF-alpha in the CSF is high and probably responsible for many of the symptoms, is followed by a second phase in which the picture remains substantially stable, there are no interferon-related symptoms and the concentration of INF-alpha in the CSF returns to normal.
How it is diagnosed

In spite of the recent important advances in the genetics of AGS, it is nevertheless important, given that there is still a considerable proportion (around 17%) of cases in which genetic analysis is uninformative, to bear in mind the clinical and neuroradiological criteria fundamental for a diagnosis of the syndrome.

Some of these criteria are "age-specific" or rather "evolution-specific", meaning that the significance of their presence or absence is different in different stages of the disease. For example, at onset of the symptoms, the presence of cerebral calcifications, while very frequent, is not an indispensable diagnostic criterion: if they are absent, patients should be monitored, over time, to see if they appear; in the same way, the absence of raised INF-alpha levels in the CSF some years after the clinical onset of the disease does not exclude a diagnosis of AGS, given that INF-alpha levels fall progressively over time.

Since cerebral calcifications are not readily identified on MRI (even though this technique is routinely used in the diagnostic workup), it is important to remember to perform brain CT scans, to look for them, in all cases of unexplained early-onset leukoencephalopathy.

These considerations apart, the main criteria for a diagnosis of AGS are:
1. Early-onset encephalopathy with psychomotor delay, spasticity, extrapyramidal signs and microcephaly, the latter appearing in the course of the first year of life;
2. Cerebral calcifications, particularly visible at basal ganglia level (putamen, pallidus and thalamus) but also extending to the white matter;
3. Cerebral white matter abnormalities;
4. Cerebral atrophy;
5. Exclusion of pre-/perinatal infections, in particular the TORCH complex (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus);
6. Chronic lymphocytosis (>5 cells/mm$^3$) on CSF examination, not accompanied by any other sign of an infectious process;
7. Raised INF-alpha in the CSF (>2 IU/ml);
8. Elevated neopterins and biopterins in the CSF, sometimes associated with decreased folates;
9. Important systemic symptoms in the early stages of the disease, for example irritability, feeding and sleeping difficulties, unexplained fevers, and the appearance of chilblain-like skin lesions on the fingers, toes and ears;
10. Genetic screening for mutations in the four genes known to cause AGS allows definitive confirmation of the diagnosis in the majority (83%) of cases.
Prenatal diagnosis

Since AGS is, with rare exceptions, inherited as an autosomal recessive trait, most couples with an affected child have a 25% risk of the disease recurring in each future pregnancy. The rare cases in which it is inherited as an autosomal dominant trait (heterozygous TREX1 mutation) appear to be sporadic and attributable to de novo mutations.

Today, genetic tests allow us to confirm the AGS diagnosis in a large proportion of cases. However, it is important to note that diagnostic prenatal testing is possible only in families that already have an affected child, in whom the disease-causing gene has been identified. If the affected child’s mutation is known, then the DNA of foetal cells obtained by chorionic villus sampling (at 10-12 weeks of gestation) or by amniocentesis (15-18 weeks of gestation) can be examined for the presence of the same mutation.

Differential diagnosis

Once congenital infections belonging to the TORCH spectrum have been ruled out, the first step in the differential diagnosis of AGS is usually to exclude other conditions in which basal ganglia calcifications are associated with early-onset encephalopathy.

It is worth pointing out that some cases described in the literature as independent clinical entities seem to fit the picture of the early-onset neonatal forms of AGS, for example, many of the cases designated MICS (microcephaly-intracranial calcification syndrome) or “pseudo-TORCH syndrome”, and also the cases referred to as “familial systemic lupus erythematosus”.

The main forms to be taken into consideration in the differential diagnosis of AGS are Cockayne syndrome, mitochondrial encephalopathies, haemophagocytic lymphohistiocytosis, and metabolic encephalopathies with basal ganglia calcifications such as, for example, parathormone metabolism disorders, biotinidase
deficiency, 3-hydroxyisobutyric aciduria, Hoyeraal-Hreidarsson syndrome, and cerebroretinal microangiopathy with calcifications and cysts (CRMCC).

**Treatment and management of patients**

Treatment of AGS is currently only symptomatic and includes the use of drugs to control epilepsy, the prevention of complications and postural abnormalities, respiratory physiotherapy to treat lung infections, and dietary monitoring to ensure adequate caloric intake. The use of botulinum toxin and myorelaxant drugs to treat the spasticity is still debated on the grounds that in AGS spastic hypertonus is, in any case, a problem that will tend to recur in the future.

Patients must be regularly screened for the symptoms of the disease which are treatable. These symptoms, sometimes present, include glaucoma and endocrine problems (e.g. diabetes or hypothyroidism). As regards the chilblain lesions, neither vasodilators nor immunosuppressants have shown any real therapeutic efficacy in AGS and the treatment of these symptoms is limited to protecting the vulnerable parts from the cold and preventing infections that could complicate the situation. In accordance with the suggestions advanced by Blau in 2003, oral treatment with folic acid might produce a general improvement of the clinical conditions in selected AGS patients presenting reduced folates in the CSF, but there are as yet no data in the literature confirming this hypothesis.

Given the involvement of the immune system and of immune system activation as a pathogenetic mechanism in AGS, it has been suggested that high-dose corticosteroid therapy might alter the course of the disease: however, to date, the attempts made have not produced significant results.

Similarly, recent reports of cases treated with high doses of steroids or iv immunoglobulin in the active stages of the disease do not seem to show any real change in the clinical course.
Current studies aiming to clarify the mechanisms underlying the pathogenesis of AGS could lead to the development of new therapeutic strategies. These treatments may, for example, act on the pathway between the undigested nucleic acids and activation of the innate immune system, be based on drugs targeting the cells responsible for the production of cytokines, or block INF-alpha activity directly.
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For a more extensive bibliography, visit www.aicardi-goutieres.org
Glossary

MICROCEPHALY
A head circumference that is significantly lower than the mean value for the child’s sex and age (i.e. lower than the 3rd percentile on the growth chart).

PYRAMIDAL TRACTS
Also called “corticospinal” tracts, the pyramidal tracts are constituted by collections of nerve fibres that originate in the motor areas of the cerebral cortex and travel to the spinal cord. They are responsible for the voluntary control of skeletal muscles.

EXTRAPYRAMIDAL PATHWAYS
Neural pathways, excluding the pyramidal tracts, that form a network called the extrapyramidal system and are involved in motor control, coordination of movement and balance.

PYRAMIDAL SIGNS
Indicate the presence of a pyramidal tract lesion.

EXTRAPYRAMIDAL SIGNS
Indicate the presence of an extrapyramidal pathway lesion.

BASAL GANGLIA
Structures made up of groups of nerve cells (neurons) located deep in the white matter at the base of the cerebral hemispheres. The basal ganglia are the main point of origin of the extrapyramidal pathways.

SPASTIC TETRAPARESIS
Clinical picture of motor deficit affecting the upper and lower limbs and trunk, secondary to a pyramidal tract lesion.
DYSTONIC POSTURES AND MOVEMENTS
Twisting postures or movements affecting some parts of the body. Caused by involuntary and prolonged muscle contractions, they are linked to lesions or malfunctioning of the extrapyramidal system.

NYSTAGMUS
Involuntary rapid and rhythmic oscillatory motion of the eyeball.

STARTLE REACTION
Rapid reaction (like a sudden contraction or jump) occurring in response to a sudden and unexpected sensory (in particular auditory or tactile) stimulus.

WHITE MATTER
The part of the brain that lies below the grey matter. The white matter consists of bundles of both ascending and descending nerve fibres that connect the brain with the spinal cord. It is so called because of the white colour of the myelin sheath that covers the nerve fibres.

LEUKODYSTROPHY
Genetic disorder, typically of childhood, that leads to degeneration of the white matter of the brain.

CEREBRAL ATROPHY
Reduction in the quantity of brain tissue.

CEREBROSPINAL FLUID
Liquid produced in the ventricles of the brain, which surrounds and fills the spaces in the brain and spinal cord. It exerts a protective function, both mechanical and immunological. It contains percentages of protein, glucose and cells.
INTERFERON-ALPHA
A protein belonging to the cytokine class of proteins. Normally produced by the innate immune system in response to an insult by external agents, e.g. viruses, it serves to inhibit their replication and diffusion. Secretion of interferon-alpha can lead to the appearance of symptoms such as fever, a feeling of being unwell, muscle weakness.

HEPATOSPLENOMEGALY
Increase in the volume of the liver and spleen.

CHILBLAINS
Skin lesions (often hereditary) that appear following exposure to the cold, in particular to the cold and damp. Chilblains are characterised by the presence of shiny red areas on cold skin, and they appear mainly on the fingers, toes and ears. They can be painful and sometimes itchy.

CHROMOSOME
The structure containing human DNA. The human cell nucleus contains 46 chromosomes (23 pairs) transmitted in equal measures (23+23) by the mother and father.

DNA
Double-stranded molecule (also called the double helix) that carries our “genetic code”: in other words, it contains all the coded information that, through the synthesis of proteins, determines the characteristics and functioning of our organism.

GENE
Portion of DNA that codes for a protein. Every gene determines a specific hereditary characteristic. Humans have two copies of each gene, one copy inherited from the mother and the other inherited from the father.
LOCUS
The position of a gene in the chromosome; although the locus indicates the area of the chromosome, and thus of the DNA, in which a given gene is located, it does not identify its position exactly.

MUTATION
An alteration in the genetic material (DNA) which can potentially modify genes. When such an alteration occurs, production of the protein encoded by the gene containing the mutation can also be altered. This can lead to different effects on the organism, depending on the function of the affected protein.

AUTOSOMAL RECESSIVE INHERITANCE
A pattern of disease transmission. A disease is inherited as an autosomal recessive trait only when mutations are present in both copies (one for each chromosome) of the gene responsible for the disease. The parents of a child with an autosomal recessive disease are healthy, but they are carriers of a mutation of the gene for that disease (i.e., they have one mutated copy of the gene and one that is normal).
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