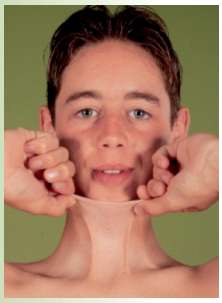
# **E**hlers-**D**anlos **S**yndrome

**Sections of this chapter were written with the collaboration of the Association Française des Syndromes d'Ehlers Danlos and Associazione Italiana per la Sindrome di Ehlers-Danlos (A.I.S.E.D.).**

## **Clinical** Picture

Ehlers-Danlos syndrome (EDS) is a group of diverse genetic disorders caused by a mutation leading to the body's inability to produce collagen. Collagen is a protein required for the synthesis of connective tissue that makes up ligaments, tendons and cartilage and is responsible for the strength and elasticity of skin and blood vessels. The syndrome is usually inherited via an autosomal dominant mode of transmission, however in some cases transmission can be autosomal recessive or X-linked recessive. There are several subtypes of EDS and symptoms vary widely depending on the type. In the classic forms (formerly known as EDS types I and II) symptoms include unstable, flexible joints with a painful tendency to dislocate, joint pain, fragile hyperelastic skin that scars and bruises easily and hiatal hernias. Symptoms that occur in rarer forms of EDS include pulmonary problems and high risk of blood vessel or organ rupture (vascular type, formerly EDS IV); congenital hip dislocation (arthrochalasia type, formerly EDS VIIB); gum disease (EDS VIII); curvature of the spine and serious eye conditions (kyphoscoliosis type, formerly EDS VI) and problems with blood clotting.



**Patient, Ehlers-Danlos**
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The overall prevalence of EDS is estimated at one per 10 000 individuals and certain types affect females more than males. The age of onset of EDS is neonatal or during infancy. Prognosis for people with EDS depends largely upon the type of EDS. Some individuals have negligible symptoms while others are severely restricted in their daily life. Most individuals with EDS will have a normal lifespan; however, this is shortened in those with vascular type EDS due to the dangerous rupture of blood vessels and organs. Currently, there is no cure for EDS and treatment includes the management of symptoms and the prevention of further complications through physiotherapy and the use of pain relievers and devices that support the musculoskeletal system.

## **Living With** Ehlers-Danlos Syndrome

Every person experiences EDS differently. For some, symptoms can appear in childhood at a time when mobility begins but stability and strength are not yet fully developed. As a result, frequent spontaneous bruising, joint

dislocations and open wounds that take a long time to heal can occur, hindering the enjoyment of playing, sports and movement in general. Due to the nature of the syndrome, children may have to miss school for medical care, social services, or chronic pain and flare-ups of other symptoms. At school, children may tire easily requiring extra time to accomplish tasks. They may also use supportive splints to aid stability, making activities even more difficult. Children who need to overcome these difficulties may develop psychological and emotional problems. As EDS is a hereditary condition, children with EDS may come from a family where one parent lives with similar difficulties.

EDS in adults can present additional complications with aging. Some adults begin life with no symptoms; they finish studies, start families and build careers. EDS in adulthood can significantly disrupt established life routines with the onset of chronic pain and fatigue throughout the entire body. Serious injuries such as the rupture of arteries, colon or uterus are not only life-threatening; they may also contribute to a patient's anxiety. Great effort must be taken to conserve energy by careful planning to accomplish tasks. Management and care of joints introduces additional challenges, requiring people with EDS to use their joints with caution, maintain good posture, keep off their feet whenever possible (i.e. while showering, dressing) and avoid heavy lifting or unnecessary effort (i.e. a continuous level working space in the kitchen to allow items to be pushed instead of lifted, a car with automatic transmission and power steering, and ironing only what is absolutely necessary). Chronic pain, if not correctly controlled, can lead to stress and depression. People with EDS may also experience extreme frustration with the fact that, although it is a debilitating condition, EDS symptoms are not necessarily visible to family, friends, colleagues and doctors, who insist that what a patient is feeling is 'all in their mind'.

'My whole body is in constant pain so I need assistance all the time: with opening doors, carrying heavy bags and even getting in and out of the car takes guts.' Ritva, 44, Finland

## **Diagnosis** of Ehlers-Danlos Syndrome

### PARTICIPANTS IN THE SURVEY

Responses from 414 families of EDS patients from five countries were analysed in the survey *(Figure 1)*. Females made up 82% of respondents and males 18%. One half of the patients were diagnosed at 29 years of age (and 25% prior to 13 years and 25% after 41 years).

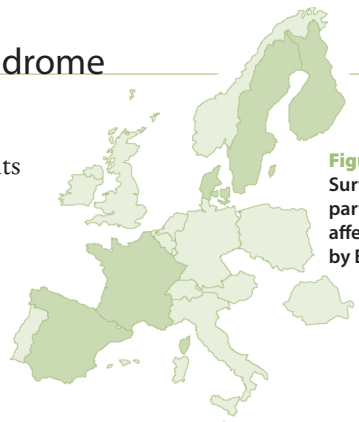

**Figure 1**
**Survey participants affected by EDS**

### AWAITING DIAGNOSIS

A period of 14 years elapsed between the first clinical manifestations of the disease and diagnosis for half of patients (28 years for 25% of the latest diagnoses). This delay was longer for females (an average of 16 years) than for males (an average of four years). During the quest for diagnosis, more than five physicians were consulted by 58% of patients and more than 20 physicians by 20% of patients (as compared to 25% and 4%, respectively in the overall

survey population). A significant number of different examinations and tests (biological tests, 62%; X-rays, 61%; functional testing, 45%) were performed to reach the correct diagnosis. Before obtaining the correct EDS diagnosis, a misdiagnosis was given to 56% of patients (including a psychiatric diagnosis in 20% of these patients).

'One day I counted that I received 32 incorrect diagnoses before the correct one. They ranged from "You have nothing" to "It's all in your imagination" to very severe ones, like cancer. Some doctors told me I could live a normal life, others told me I was going to die.' Dolores, 49 years old, Spain



## CONSEQUENCES OF DELAYED DIAGNOSIS

Misdiagnoses resulted in inappropriate treatment in 70% of the patients (medical, 30%; surgical, 17%; or psychiatric, 7%). In addition, misdiagnosis was associated with a longer time to reach a diagnosis of EDS (eight years without misdiagnosis, 19 years with somatic misdiagnosis and 22 years with psychiatric misdiagnosis). For 86% of the patients, the delay in diagnosis was considered responsible for deleterious consequences *(Figure 2)*.

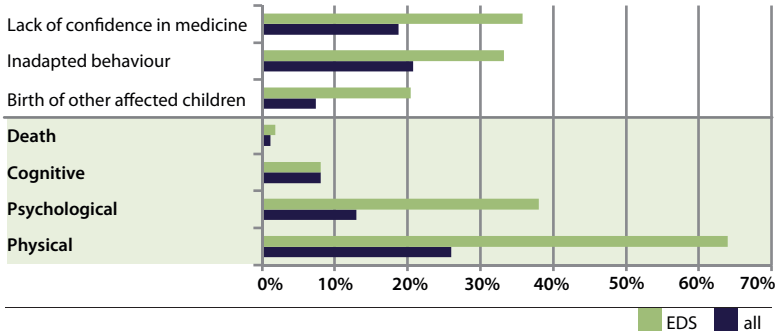


**Figure 2**
**Consequences of delayed diagnosis for respondents affected by EDS**

## DIAGNOSIS

Diagnosis of EDS in the 414 EDS patients was obtained on the basis of clinical (41%), biological (20%) and functional (14%) data. The structure providing the diagnosis was a specialised centre (61%) or another hospital structure (61%) located in another region or country for 37% of patients, and for which contact details were obtained from non-medical sources in 37% of cases. Access to diagnosis required a financial contribution from 58% of patients and was considered as a low or moderate contribution by two-thirds of these respondents and high or very high by one-third. For 25% of patients, the time for reaching diagnosis depended, at least partially, on the personal cost. A second opinion was sought by 31% of patients to confirm the diagnosis (as compared to 21% overall).

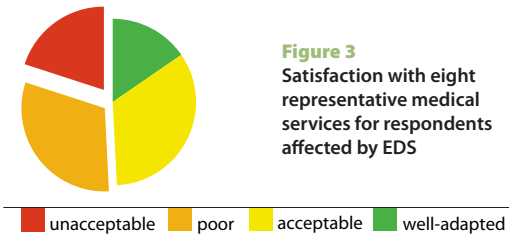


**Figure 3**
**Satisfaction with eight representative medical services for respondents affected by EDS**

## ANNOUNCEMENT OF DIAGNOSIS

Diagnosis was most often given by a geneticist (55%) or directly received from a diagnostic laboratory (29%). Communication of the diagnosis occurred during a standard private consultation in 68% of cases, but also occurred orally in another manner (e.g. informally in the corridor) in 15% of cases or in written form without explanation (4%).

'As EDS is a hereditary disease, you always have to take into account that if you have children, they may inherit the disease.' Dolores, 49 years old, Spain

For 34% of patients, the diagnoses were given without information on the disease even though 98% of patients considered that this information should be systematically provided. Psychological support accompanying the announcement of diagnosis was infrequent (19%), and when available was provided by a health professional (11%) or a patient organisation member (4%). Despite this low level of psychological support, 98% of families thought it should be systematically offered. The genetic nature of the disease was explained to families in 67% of cases, with details about the possibility of other members in the family having the same disease in 58% of cases. Genetic counselling was provided to 26% of patients. Whether based on the suggestion of a health professional (26%) or not, the patient communicated this information to other members of the family in 85% of cases, either to the parents (55%), grandparents (23%), siblings (61%), or uncle, aunt or cousin (34%). This communication resulted in diagnoses in relatives already having symptoms in 31% of cases.



## **Reactions** to Results

Although the disease can affect men and women equally, women are more often members of patient organisations, possibly because they are more available and motivated to seek help. They are, however, often diagnosed later because their pain and hypotonia are not considered as physical symptoms but rather as psychological symptoms or common complaints. During the search for diagnosis, much help and support comes from relatives and family. Patients often report rejection by doctors, who refer them to another specialist equally unfamiliar with the disease to 'rid' themselves of the complicated case. This results in a loss of hope followed by bitterness and anger. Many patients turn to alternative medicine in order to receive the proper attention they deserve. When EDS patients are misdiagnosed, it is often up to them to seek another opinion because the disease does not progress, thus the doctor does not question the initial diagnosis. Incorrect psychiatric diagnoses cause the greatest frustration amongst patients and result in disappointment, anger and mistrust toward the health system for all the time lost. When an EDS diagnosis is finally reached, the possibility of a second opinion is rarely suggested and if sought, often leads to a break in the relationship with the first doctor. Initially, the announcement of an EDS diagnosis can be a relief. Unfortunately, the announcement is rarely accompanied by more detailed written information about the disease, crucial for a patients' understanding. Acceptance of the diagnosis can later be difficult and requires a certain amount of time and discussion with a trusted doctor.

## **Access to Medical** and **Social Services**

**PARTICIPANTS IN THE SURVEY**

Responses from 822 families of EDS patients from 12 countries were analysed in the survey *(Figure 4)*.

**Figure 4** Survey participants affected by EDS

Respondents were mainly female (84%). The mean age of patients was 41 years (the mean age at diagnosis: 28 years).

### NEED FOR MEDICAL SERVICES

Overall, each patient with EDS required an average of 12 different kinds of medical services in relation to their disease (three more than the average number of services required by the 16 rare diseases surveyed).
In addition to the consultations listed in Figure 5, orthopaedics (42%), ophthalmology (40%), rehabilitation medicine (33%) and emergency services (30%) were also frequently needed. Gynaecology, podiatry, ear-nose-throat medicine, gastroenterology, genetics, internal medicine, psychiatry, neurology, pulmonary medicine, oral and maxillofacial medicine and nutrition services were required, in decreasing frequency, by 29% to 14% of patients. The most frequently required explorations were biological testing (57%), radiology (49%), specialised imagery (41%) and electrocardiogram (37%), but also functional testing (26%), biopsy/cytology (24%), microbiology (20%), ultrasound (18%) and genetic testing (10%). As for other types of care, glasses (44%), nursing care (23%), injections (22%), occupational therapy (19%) and prostheses (17%) were the most needed. Hospitalisation occurred in 51% of patients for an average total duration of 17 days.

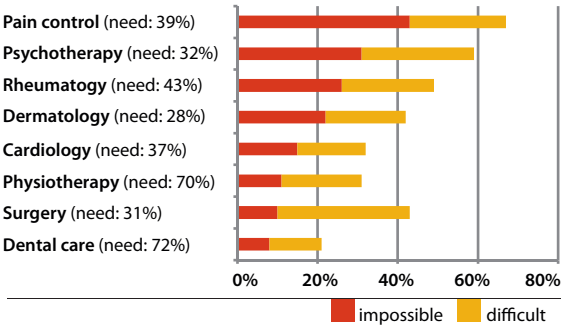


**Figure 5**
**Need for and access to eight essential medical services for Ehlers-Danlos syndrome.**

### ACCESS TO MEDICAL SERVICES

**Lack of access to medical services in 18% of situations overall for EDS patients**
Impossible access to services was most frequently reported for pain control services (43%), psychotherapy (31%), rheumatology (26%) and dermatology (22%), followed by cardiology (15%), physiotherapy (11%) and surgery (10%). A lack of referral was the most frequent cause for lack of access to dermatology (70%), pain control (67%), cardiology (61%), rheumatology (55%) and surgical (42%) consultations. Unavailability was the predominant cause for lack of access to psychotherapy (44%) and physiotherapy (43%) services. Impossible access to dental care was most frequently due to personal cost (56%). Waiting time for obtaining an appointment was considered a hurdle to access to rheumatology (33%), cardiology (26%), physiotherapy (24%), psychotherapy (24%) and pain control services (23%). Long waiting times prevented access to rheumatology services for one out of three patients, and to cardiology, pain control, psychotherapy and physiotherapy services for one out of four patients. Access issues related to the distance from the medical structure

included difficulty in travelling to access physiotherapy (29%), rheumatology (24%), dermatology (20%) and cardiology (20%) services, and the inability to find anyone to go with (14% to 22% of respondents for the eight surveyed medical services).

**Access to medical services was difficult in 23% of situations**

Difficult access was significant for surgery (33%), pain control services (24%), psychotherapy (28%), rheumatology (23%), dermatology (20%) and physiotherapy (20%) services, followed by cardiology (17%) and dental care (13%). An insufficient number of appointments were reported for pain control, rheumatology, psychotherapy and physiotherapy in more 30% of situations. Personal cost was considered excessive for the eight medical services — in 29% to 33% of cardiology, physiotherapy, pain control and surgery consultations, and to an even larger extent for rheumatology (37%), psychotherapy (43%), dermatology (44%) and dental care (56%).
Despite evident difficulties in travel, the assistance of a professional for the journey to the medical structure was scarce, overall 9%, and was most often provided for pain control (18%) and surgical (14%) services.
Time for obtaining appointments was considered long or very long by 57% of patients for pain control (on average 11 months), 53% for rheumatology, 44% for dermatology, 41% for surgery (six months), 39% for psychotherapy and 34% for cardiology services.

**Satisfaction with medical services**

Overall, 81% of patients considered that medical services, when obtained, responded fully or partially to their expectations, representing the lowest level of satisfaction for the 16 surveyed rare diseases, with wide variability between services: 92% for dental care, 89% for cardiology, 72% for pain control and 70% for rheumatology *(Figure 6).*

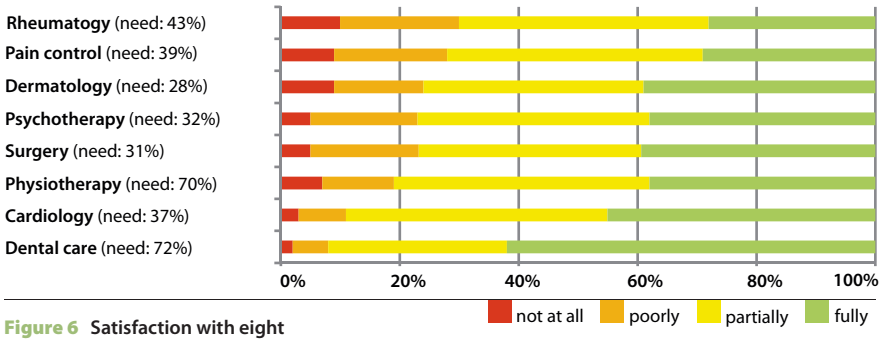


**Figure 6** **Satisfaction with eight representative medical services for respondents affected by EDS**

## SOCIAL ASSISTANCE

Amongst the 32% of families needing social assistance, 9% failed to meet with a social worker and 38% met one with difficulty.
When obtained, the level of satisfaction with social assistance was significantly low, overall less than 30% *(Figure 7).*

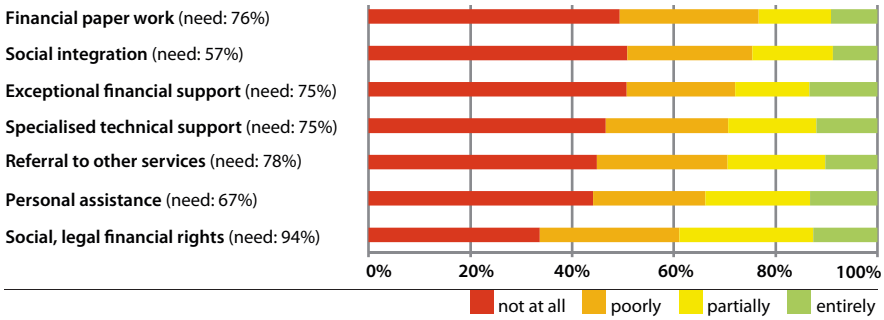


**Figure 7** **Satisfaction with specific social services for respondents affected by EDS**



## REJECTION

Patients with EDS experienced rejection by health professionals very frequently (35%); this is twice the level observed overall for the 16 surveyed rare diseases (18%). The reluctance of health professionals due to the complexity of the disease was reported by almost all rejected patients (95%). In addition, patients were rejected for personal reasons, including difficulties in communication (10%), physical aspects (8%) or disease-related behaviour (5%). Even if the rejection was mainly linked to the disease rather than the patient, its extent was perceived as the health professional's refusal to treat EDS patients. The frequency and cause of rejection varied according to the patient's country of origin *(Figure 8)*.

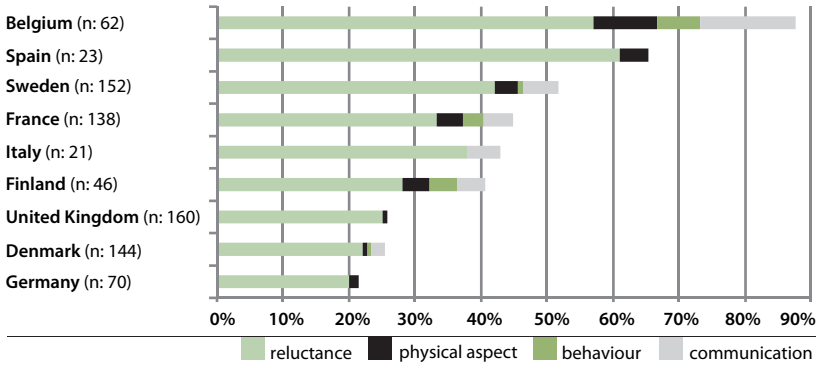


**Figure 8** **Cumulated frequencies of causes of rejection by country (n: total number of respondents) in EDS. As patients may have been rejected more than once for more than one reason, the total number of rejections exceeds the number of rejected respondents.**

## CONSEQUENCES OF THE DISEASE

As a consequence of the disease, 22% of patients had to relocate. Amongst them, 75% moved to a more adapted house and 21% moved to be closer to a relative, i.e. for day-to-day support not provided by the social or healthcare system. As a consequence of the disease, 60% of patients with EDS had to reduce or stop their professional activity. In addition, in 8% of families one member reduced or stopped professional activities to take care of a relative.

## EXPECTATIONS REGARDING CENTRES OF EXPERTISE

Not differing from the overall opinion of survey participants, respondents with EDS considered the following functions provided by a centre of expertise as the four most essential:

- Coordinating the sharing of medical information on the patient between all professionals who care for him/her in the specialised centre
- Communicating with other specialised centres and professional networks to harmonise treatments and research at the national and European levels
- Coordinating the sharing of medical information between professionals of the specialised centre and local professionals, to facilitate the continuity of the patients' follow-up
- Collaborating with research teams working on the rare disease (in particular for clinical studies)

Survey participants with EDS considered 'training local professionals in responding to the specific needs of patients and supplying their contact information to patients' as the fifth most essential function provided by a centre of expertise; a much higher ranking of priority than expressed by all other respondents. As EDS patients reported rejection by healthcare professionals most frequently amongst all the investigated diseases, it is not surprising that training non-specialist local healthcare professionals in their disease-specific needs is considered important. Compared to respondents overall, respondents affected by EDS more often expressed that 'the main hurdles in travelling to a specialised centre are the time needed to get there and/or physical difficulties encountered by the patient (pain, fatigue and injuries)'.



## **Reactions** to Results

The complexity of EDS results in a need for many different medical services and sometimes hospitalisation during the diagnostic phase. In addition to the eight essential medical services investigated in the study, rehabilitation medicine should also be added to the list. Lack of access to these services is most often due to a lack of referral by doctors, who have insufficient knowledge of the disease and its needs. Services dedicated to pain or genetic diagnosis exist, however patients are often not referred to them. In the absence of specialised centres or hospitals with expertise in EDS, patients go to private specialists at their own expense. All too often the medical services are not adapted to the needs of EDS patients; in particular they do not take into account how severely symptoms affect the quality of life.
The frequency and reasons for rejections by health professionals described in the survey correlate well with patient organisation reports. Doctors, in particular specialists, most often refuse to treat a patient because of the complexity of the disease.
There is a great need for social services due to the disability caused by EDS. Unfortunately, the lack of recognition of the disability and inadequate number of social services adds to the difficulty in accessing them. EDS patients must frequently rely on themselves to adapt their homes or to find new appropriate accommodation that allows them to maintain independence. Very often the disease forces patients to interrupt or significantly reduce professional activities with no economic assistance. Similarly, family members may stop working in order to take care of a relative when funding or professionals for daily support are not available.