INTRODUCTION

The International Consortium on the Ehlers–Danlos Syndromes

LARA BLOOM,* PETER BYERS, CLAIR FRANCOMANO, BRAD TINKLE, AND FRANSISKA MALFAIT ON BEHALF OF THE STEERING COMMITTEE OF THE INTERNATIONAL CONSORTIUM ON THE EHLERS-DANLOS SYNDROMES

Since 1998, two developments have led to concerns that the EDS nosology needs to be substantially revised. The first development was the clinical and molecular characterization of several new EDS variants, which substantially broadened the molecular basis underlying EDS. The second was the growing concern, in the absence of genetic diagnosis, that the hypermobile type of EDS had an expanded phenotype, may be genetically heterogeneous, and that the diagnostic criteria currently in use were inadequate. Furthermore, there is a dire need for the development of guidelines for management for each type of EDS to allow both the specialist and the generalist to care for affected individuals and their families. We have been meeting together as an international consortium over the past 2 years to establish these new criteria and management and care guidelines

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INTRODUCTION

The Ehlers–Danlos syndromes (EDS) have fascinated people throughout the ages. The first report of this disorder dates back to Hippocrates (fourth century BC). For many centuries, affected individuals earned their livings as The Elastic Skin Man, The India Rubber Man and The Human Pretzel, amazing their audiences in fairgrounds and circus side shows by exhibiting contortionist tricks and a remarkable ability to stretch their skin. Job Janszoon van Meek'ren [1657] provided a first partial description, but the first classical description of the syndrome in the medical literature is attributed to Tschernogubow, a Russian dermatologist in 1891 [Tschernogubow, 1891; Denko, 1978]. In 1901 and 1908, respectively, the Danish and French dermatologists Edvard Ehlers [Ehlers, 1901] and Henri-Alexandre Danlos [Danlos, 1908] identified people with striking alterations in the mechanical properties of the skin and in the 1930s the condition received its eponymous title, and, by this, its scientific respectability [Parkes Weber, 1936]. In the mid-20th century it was suggested that a genetic defect in the collagen "wickerwork" of the connective tissues probably accounted for the phenotype and not much later the first genetic defect was identified as a deficiency of lysyl hydroxylase, a collagen modifying enzyme [Krane et al., 1972].

The Ehlers–Danlos syndromes are classically defined as a heterogeneous group of heritable disorders of connective tissue characterized by articular hypermobility, skin hyperextensibility

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and tissue fragility affecting skin, ligaments, joints, blood vessels, and internal organs [Steinman et al., 1990]. Classification of this clinically and genetically heterogeneous group of conditions began in the late 1960s. Barabas [1967] and then Beighton [1970] recognized sufficient diversity in the clinical presentations and natural history to delineate five apparently discrete types of EDS. In 1986, a nosology was proposed at a meeting in Berlin, which formalized the nomenclature of the various types [Beighton et al., 1988]. In the Berlin Nosology, eleven subtypes were recognized and each subtype was designated a Roman number. Developments in the elucidation of the biochemical and molecular bases of EDS, together with increasing clinical experience, permitted refinement of the nosology, leading to the Villefranche nosology [Beighton et al., 1998]. This nosology proposed a simplified classification into six major subtypes, for which major and minorclinical criteria were defined, and substituted the previous Roman numeral types by a descriptive nomenclature.

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At the First International Meeting on EDS held in Ghent, Belgium, in September 2012, an International Consortium on EDS was formed with the objective to convene a group of clinicians, scientists and lay members of the EDS Community to come to grips with the increasingly difficult aspects of definition and management of EDS types, to define research agenda's, and to continue EDS meetings. Ehlers–Danlos Support UK (EDS UK) and the Ehlers–Danlos National Foundation (EDNF) took up the task to fund this enterprise and develop a framework in which this work could be completed. Five working committees were established, including a (i) Steering Committee (consisting of the chairs of each of the other four committees, a representative from EDS UK and EDNF and a representative from OMIM), and committees on (ii) classical EDS, (iii) hypermobile EDS, (iv) vascular EDS, and (v) rare subtypes of EDS. Since it has become clear that the clinical characteristics of many of the types of EDS extend well beyond the realms of skin and joints, specific working groups (pain, fatigue, cardiovascular, gastrointestinal, orthopedic, oromandibular, physical therapy, Beighton scoring, neurology, allergy/immunology, psychological aspects) engaging specialists from all areas of medicine, were organized to review specific manifestations and formulate recommendations. Each committee and working group were made up of several specialists representing multiple countries and disciplines as well as had representation from the patient support groups worldwide.

The type-specific committees were charged with performing a comprehensive review of the literature and defining the nosology and diagnostic criteria of each EDS type. The working groups also were charged with reviewing the literature with a further focus on management. Each group was also charged in identifying the areas of needed research. These groups met in person or through tele/videoconferencing on a regular basis over a two-year timespan.

The proposed criteria, literature review and recommendations were presented to other professionals working in the field during an International Symposium on the Ehlers–Danlos Syndrome in New York, in May 2016, and manuscripts were subsequently circulated for critical review. The work presented in this issue of the American Journal of Medical Genetics, Seminars in Medical Genetics represents the consensus of the group after critical review of the literature and considering the professional experience of each of the authors.

The Consortium is the beginning of a process that should be ongoing. It will (i) identify a set of participants that can revise the classification on an ongoing basis, (ii) implement both general and type specific registries to help better define the natural history, medical history, and epidemiology of EDS, (iii) be the basis of periodic international scientific meetings to advance recognition and treatment, and (iv) support smaller disorder specific meetings to focus on advances and to define needs for research. This effort will continue forward with the support of the newly formed international charity The Ehlers–Danlos Society, which was established with this mission at its forefront.

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