MDH Minnesota Department of Health
OFFICE OF MEDICAL CANNABIS

Ehlers-Danlos Syndrome

SEPTEMBER 2016

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Ehlers-Danlos Syndrome (EDS) is a group of inherited connective tissue disorders. They are conditions distinct in clinical features and, where known, genetic basis. Genetic alterations in production of collagen and other components of the extra-cellular matrix as well as in cellular signaling contribute to the clinical features of EDS. Advances in genetic research have rendered the standard classification of EDS, the 1997 Villefranche classification, in need of revision, but it is still in widespread use. The Villefranche classification delineates six types of EDS. Of the six, the following three are by far the most common (Sobey 2014):

Classical EDS

Joint hypermobility, marked skin hyperextensibility, and widened atrophic scars are its hallmarks. There are also a number of typical skin findings. As with all types of EDS, pain in joints and elsewhere in the musculoskeletal system can be severe. Mutations in type V collagen cause classical EDS. It is dominantly inherited, though severity can vary within the same family.

Hypermobile EDS

Generalized joint hypermobility with recurring joint dislocations and hyperextensible skin are the characteristic manifestations. Severe chronic joint pain coupled with symptoms of autonomic dysfunction (example – heart rate changes that can lead to fainting when moving to a standing position) can severely impair quality of life and limit opportunities for education and employment. Muscle cramps, headaches, and fatigue are frequently present (Rombaut 2010). The genetic basis of Hypermobile EDS is unknown. The higher prevalence among women remains unexplained.

Vascular EDS

Structural anomalies in blood vessels – including large blood vessels such as the aorta – make rupture of vessels and of hollow organs (colon, for example) a particular risk for this type of EDS. The skin, rather than being hyperextensible, is thin, translucent, and prone to easy bruising. Joint hypermobility is usually limited to small joints in the hands. Vascular EDS is caused by a gene that codes for type III collagen.

Musculoskeletal pain is a prominent symptom of patients with EDS but the pathophysiology of the pain – the chain of causes that leads to the pain – is not well defined. There are likely multiple causes, including biomechanical/physical determinants, deconditioning, and neurological mechanisms (Scheper 2015). Generalized joint instability may cause the occurrence of micro-traumas on joint surfaces, leading to adaptation and compensation of movement patterns, causing areas of overload on other joints and muscles. Soft tissue laxity could contribute to overload of tendons. Pain could lead to decreased activity resulting in weakness of muscles and loss of proprioception information (position of joints and limbs) causing changes in movement patterns. Research presents some evidence of brain and spinal cord changes leading to increased sensitivity to pain.

Some of the substantial disability in EDs patients might be due to pain-related fear. Fear of pain might trigger avoidance of painful muscle contractions, leading to submaximal muscle performance, resulting in reduction of the force needed to stabilize hypermobile joints. This could lead to a downward spiral of impaired balance, loss of confidence, and further fear of movement and pain (Scheper 2015).

Prevalence

A widely stated estimate of prevalence of Ehlers-Danlos syndrome is 1 in 5,000 persons. This comes from a book chapter on EDS that cites a wide range of estimates of EDS and gives the 1 in 5,000 as the authors' best guess (Steinmann 2002).

Current Therapies

No curative therapy is available for EDS, so treatment focuses on relieving symptoms and preventing serious complications. EDS affects multiple body systems and typically EDS patients benefit from a coordinated, multi-disciplinary approach to care. Key aspects of care include physical therapy and occupational therapy, pain management, cardiovascular assessment, and psychological care (Rombaud 2010). Though pain management is well recognized as important for managing patients with EDS, published articles found did not go into detail about specific clinical approaches for EDS – other than to discuss the familiar, untoward side effects that accompany use of opioid drugs.

Pre-Clinical Research

The pathogenesis of musculoskeletal pain in EDS patients is currently not well-defined. Accordingly, it is not clear what aspects of endocannabinoid system investigations are most relevant for musculoskeletal pain in EDS patients. No published articles were found that focused specifically on animal models of EDS.

Clinical Trials

No clinical trials were found in the published literature or on ClinicalTrials.gov for studies of cannabis or cannabinoids as therapy for pain or other symptoms in patients with EDS. For purposes of pain management and muscle spasm reduction, published clinical trials in these areas might be applicable. The degree to which each study is relevant to patients with EDS isn't clear however, given the unknowns about the pathogenesis of musculoskeletal pain in this population. Summaries of clinical trials of cannabis and cannabinoids for pain and for severe, persistent muscle spasm can be found in a document maintained by the Office of Medical Cannabis: *A Review of Medical Cannabis Studies Relating to Chemical Compositions and Dosages for Qualifying Medical Conditions*.
http://www.health.state.mn.us/topics/cannabis/practitioners/compdosagerpt.pdf

Observational Studies

No published observational studies were found related to use of cannabis or cannabinoids as therapy for pain or other symptoms in patients with EDS. There are however,

many testimonials and accounts of benefits from use of cannabis in EDS patients on web sites maintained by individuals and by organizations.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the treatment of Ehlers-Danlos Syndrome were found.

References

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