



EHLERS-DANLOS EXPERT PANEL REPORT

FINAL REPORT

Report to The Ministry of Health
and Long-Term Care

Prepared by: Critical Care Services Ontario | December 3, 2015



CCSO Critical Care Services Ontario

Section 1.0 – Overview

1.1 Ehlers-Danlos Syndrome in Ontario

About Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a genetically inherited disease that includes a heterogeneous group of connective tissue disorders caused by various defects of collagen metabolism¹. According to the literature, 1 in 5000 people live with EDS². The most frequent presentations of this condition are characterized by joint hypermobility and instability, widespread musculoskeletal and/or nervous system acute and chronic pain, skin hyperextensibility, and tissue fragility^{3 4}. Based on genetic abnormalities and clinical manifestations of the disease, EDS is described by six main types, namely: Classic, Hypermobility, Vascular, Kyphoscoliotic, Arthrochalasia, and Dermatosparaxis. The most prevalent subtypes of EDS are Classic, Hypermobility and Vascular⁵, accounting for 79% of the EDS population. The Classic type is due to a mutation of the COL5A1 or COL5A2 genes and can be confirmed by clinical evaluation and/or genetic testing. The Hypermobility type presents with similar clinical features to the Classic type, however, the genes affected for Hypermobility type are largely unknown⁶. Together, the Classic and Hypermobility types account for 75% of the EDS population. The third most prevalent type of the syndrome is the Vascular Type (affected gene COL3A1), with the prevalence of this EDS type decreasing substantially to 1 in 250,000. There is no known cure for EDS.

A commonly expressed patient experience among the EDS population and by treating physicians is that the condition is “difficult to diagnose”. Since the condition affects multiple systems, such as the nervous and/or orthopedic system, skin, joints, blood vessels, and internal hollow organs, clinical presentation can vary widely from patient to patient. It can therefore be challenging to provide an accurate diagnosis given the overlapping symptomatology. This, combined with the rarity of the disease, can result in multiple and prolonged clinical investigations for patients. Once a diagnosis of EDS is determined, patients report challenges in accessing health care providers with knowledge of EDS in primary care and at acute care centres. To bridge this gap, EDS Advocacy groups, such as The ILC Foundation⁷ and EDS Canada, provide information via the internet and by conducting conferences. Advocacy groups maintain that additional research and health care provider education is required to support the needs of the EDS community in Ontario⁸.

Prevalence of EDS in Ontario

Based on 2015 population estimates, it is estimated that 2,762 individuals in Ontario are affected by EDS. As mentioned previously, Classic, Hypermobility and Vascular types account for almost 80% of the EDS population.

Table 1: Prevalence Estimates of Ehlers-Danlos Syndrome, by Type and by Local Health Integration Network.

LHINs	2015 Population Projections	Overall (1:5,000)	Hypermobility (1:10,000)	Classical Type (1:20,000)	Vascular (1:250,000)	Others
(01) Erie St. Clair	636,020	127	64	32	3	27
(02) South West	971,545	194	97	49	4	41
(03) Waterloo Wellington	778,683	156	78	39	3	33
(04) Hamilton Niagara Haldimand Brant	1,437,427	287	144	72	6	60
(05) Central West	921,960	184	92	46	4	39
(06) Mississauga Halton	1,229,591	246	123	61	5	52
(07) Toronto Central	1,264,038	253	126	63	5	53
(08) Central	1,874,907	375	187	94	7	79
(09) Central East	1,603,248	321	160	80	6	67
(10) South East	496,421	99	50	25	2	21
(11) Champlain	1,319,923	264	132	66	5	55
(12) North Simcoe Muskoka	475,680	95	48	24	2	20
(13) North East	564,411	113	56	28	2	24
(14) North West	235,848	47	24	12	1	10
Total	13,809,702	2,762	1,381	690	55	580

It is within the Classic and Hypermobility types that heterogeneous symptomatology presents, ranging from hypermobility and manageable pain, to frequent dislocations and joint instability. Recently, neurological manifestations in EDS have received increased attention due to the potentially disabling attributes⁹. These may include brainstem and spinal cord symptoms characterized by cervico-medullary syndrome, cranio-cervical instability and kyphosis of the clivo-axial angle¹⁰. Other neurological manifestations may include neuropathy and widespread pain, urogenital pain and dysfunctions syndrome, tethered cord, and headache. The neurosurgical capacity and capability to treat these conditions exists in Ontario, however it is reported that few EDS patients meet criteria for neurosurgical interventions to achieve clinical improvement. As a result, a number of EDS patients have sought treatment in the United States due to the assumption by EDS patients and their families that expertise was not available in Ontario.

1.2 EDS Expert Panel – Context, Membership, Mandate and Process

Context

Since 2012, the Ministry of Health and Long-Term Care (MOHLTC) has been receiving out-of-country applications requesting funding to support surgeries to treat cranio-cervical instability and spinal cord interventions, such as release of tethered spinal cord to relieve secondary symptoms, related to Ehlers-

Danlos Syndrome. Critical Care Services Ontario (CCSO) confirmed that patient reimbursements have not occurred in other Canadian provinces (such as Alberta, Nova Scotia, New Brunswick and Manitoba) for these procedures for the EDS population. Expertise to provide neurosurgical services to patients with EDS exists in Ontario, and surgical interventions for cervical spine fusion and tethered spinal cord release have been performed for EDS patients at Ontario's neurosurgical centres.

Membership and Mandate

Critical Care Services Ontario (CCSO), at the request of the MOHLTC, formed an Expert Panel (EDS Expert Panel) in late September 2015 to better understand issues related to access to care for EDS patients, and where potential improvements could be made. Co-chaired by Dr. James T. Rutka, Neurosurgeon, SickKids and Karen Kinnear, Vice President, Clinical, SickKids, the 14 member EDS Expert Panel includes representation by a variety of specialties typically involved with care for EDS patients including pain management, neurology, genetics, vascular surgery, syncope and autonomic disorders, and neurosurgery. A list of Panel Members has been Included in Appendix A. All clinical members have experience in providing treatment for patients with EDS.

The work of the EDS Expert Panel included:

- A review of providers and programs to support EDS patients in Ontario;
- A review of best-practice models in other jurisdictions;
- Analysis of potential gaps in service that may exist for the Ontario EDS patient population; and
- Provision of recommendations for an evidence-based care pathway for EDS patients, ensuring smooth transitions between paediatric and adult care settings.

Key to the mandate for the panel was establishing clarity on criteria for neurosurgical referral (along with diagnostic work up required for referral) and the criteria for neurosurgical intervention which will result in benefit to the patient.

The mandate of the EDS Expert Panel excluded any review of previous, current or future out-of-country funding request applications.

Process

Over the course of eight weeks, the EDS Expert Panel held three meetings and work by members was undertaken between meetings. A total of sixty-three articles, presentations and other published materials were reviewed (see Appendix C) to support the conclusions of the EDS Expert Panel found in the following sections: *Section 2 - Current Access for EDS Patients* and *Section 3 - Comprehensive Care Coordination Strategy for EDS Patients*.

Four members of the EDS Expert Panel also had the opportunity to attend a meeting with EDS patients and their families. EDS Expert Panel members heard first-hand about challenges with health care providers being knowledgeable about the diagnosis and treatment of EDS. This includes difficulty understanding criteria for neurosurgical interventions and potential options for alternate treatments if neurosurgical intervention is deemed not appropriate at the time.

In addition to the EDS Expert Panel Meetings, three members of the expert committee presented data, and or chaired sessions and three members of Ontario’s neurosurgical community (Drs. James Rutka, James Drake, Michael Fehlings) attended an Annual Conference “Chronic Pain Impact On Difficult to Diagnose Diseases Ruling Out Ehlers-Danlos Syndrome” on November 7th, 2015 held jointly by McMaster University and the ILC Foundation. At the Conference, the Ontario neurosurgeons attended presentations given by neurosurgeons treating EDS patients in the United States: Drs. Fraser Henderson, Harold Rekate and Petra Klinge. Following the conference proceedings on November 7th, all six neurosurgeons met to discuss indications for surgery, surgical techniques and most importantly, care co-ordination for Ontario’s EDS patients.

Section 2.0 – Current Access for EDS Patients

2.1 Programs and Providers for EDS patients in Ontario

The EDS Expert Panel identified health care specialties that are sometimes involved in the care of EDS patients. These include:

- Cardiology
- Dentistry
- Dermatology
- Gastroenterology
- General Surgery
- Genetics
- Neurosurgery/Neuroradiology
- Neurology
- Orthopaedic Surgery
- Obstetrics/Gynecology
- Ophthalmology
- Pain Management
- Psychology/Psychiatry
- Rehabilitation/Physiatry/Behavioral Medicine
- Respirology
- Rheumatology
- Syncope and Autonomic Disorders
- Urology
- Vascular Surgery

2.2 Criterion for Neurosurgical Referral (including diagnostic work-up) and Intervention

EDS Expert Panel members with experience in spine surgery formed a sub-group and, taking into consideration the interventions occurring in the US and with consultation of other neurosurgeons, orthopaedic surgeons, and neuroradiologists within Ontario, developed the following criteria for neurosurgical referral (including diagnostic work-up) and intervention. It is important to note that limited peer-reviewed clinical evidence exists in the literature to define best practices for surgical intervention for patients with EDS; therefore, these criteria have been developed based on what does exist in the literature and on consensus using suggested guidelines by the world’s leading experts in neurosurgery who have published on this topic. Given the limited available information regarding best practices, Neurosurgeons and other specialists providing care for EDS patients in Ontario will continue to

liaise with specialists in other jurisdictions, and to attend specific conferences about this rare disease to support knowledge creation, translation and adoption in Ontario.

Criteria for Neurosurgical Referral

1. Confirmed diagnosis of Ehlers-Danlos Syndrome (EDS)
 - Objective evidence to support a diagnosis of EDS completed by a genetics specialist (with genetic testing and clinical evaluation)
2. Clinical presentation to suggest cranio-cervical instability or dysfunction of the brainstem/cervical cord. Symptoms can include:
 - Cough induced headache
 - Neck pain exacerbated by flexion, lower cranial nerve dysfunction (e.g., dysphagia; dysphonia)
 - Motor dysfunction
 - Sensory abnormalities
 - Neuropathic pain
 - Gait abnormality
 - Sphincter dysfunction
3. Imaging evidence of cranio-cervical instability or dysfunction of the brainstem/ cervical cord

Diagnostic Investigations Required to Support A Referral

Evaluation to support the referral should include:

1. Flexion-extension x-rays. Evaluate for:
 - C1-2 instability; cervical kyphosis; dynamic subaxial instability
2. CT-scan: Skull base to C7. Evaluate for:
 - Anatomical abnormalities of the cranio-cervical junction (e.g., basilar invagination; platybasia)
 - Assimilation anomalies of the skull base/upper cervical spine
 - Anomalies of C1-2
 - Anomalies of the subaxial cervical spine
3. Cervical Spine MRI to evaluate for:
 - Evidence of brainstem/upper cervical cord compression
 - Subaxial cord compression
 - Chiari malformation
 - Syringomyelia

Criteria for Neurosurgical Intervention

Evidence of significant instability on dynamic imaging, with possible spinal cord/brainstem compression on MRI, and or neurological deficits to warrant a cranio-cervical fusion.

Presence of a reduced clival angle only, with tonsillar herniation, is not sufficient indication for intervention, nor should routine cranio-cervical fusion for a symptomatic Chiari Decompression be undertaken.

2.3 Neurosurgical Pathway Considerations

The number of Ontarians living with EDS, encounters with Ontario's health care system and past neurosurgical interventions on patients with EDS have been difficult to quantify due to limitations in administrative data sets (National Ambulatory Care Reporting System – NACRS and Discharge Abstract Database - DAD). Data sources show a limited number of cases with cervical fusion intervention (three cases in the past three years) and tethered spinal cord release (three cases over three years) for adult EDS patients. Additional spine surgical interventions have occurred on paediatric patients with orthopaedic intervention.

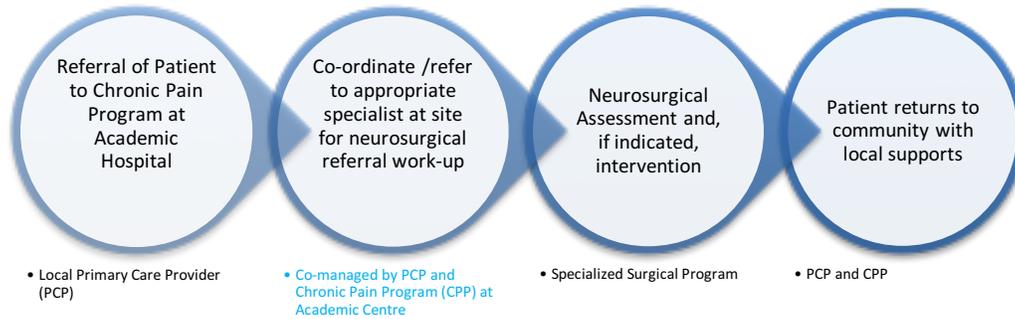
Taking into account the limited patient population in Ontario, reported data in the DAD, and the limited number of out-of-country funding requests for these interventions (five requests since 2012); the volumes of current and potential future Ontarian's with EDS requiring neurosurgical intervention is small and are within the current capability and capacity of the system in Ontario. However, given the challenges in coordination of care for EDS patients across potentially numerous providers, the MOHLTC may choose to consider centralizing access at two or three of the Province's neurosurgical centers, with subsequent access to other sub-specialty care providers. To support sufficient volumes, consideration can be given to providing assessment and intervention to EDS populations in other Canadian provinces. Interprovincial reimbursement agreements could support reimbursement for cases on a cost recovery basis. Alternatively, programs could be broadened in scope to focus on other populations within Ontario which are predisposed to cranio-cervical pathologies such as Chiari Malformations, Basilar Invagination, Morquio Syndrome, and Klippel-Feil Syndrome, among several others.

Should such a specialized program be determined to be required, based on sufficient volumes, appropriate operational infrastructure could be considered. The Expert Panel noted that the following roles would be important to form a multidisciplinary team, supporting the patient's assessment, treatment, recovery and return to their community:

- Physiotherapist
- Nurse Practitioner/Care Coordinator
- Pain Management
- Social Worker/Psychologist
- Clerical/Admin Support

Should a centralized surgical program be offered, it will be important to ensure continuity of care and recovery for the patient closer to home. The specialized surgical program would develop strong links with all chronic pain programs at academic centres across the Province so that patients experiencing pain in addition to neurological indications can be referred through the pain programs to neurosurgery and those patients having had neurosurgical intervention may return to a chronic pain centre (closer to their home) to access ongoing care for their condition.

Proposed Patient Neurosurgical Pathway



For those of the Ontario EDS population who live with chronic pain, five paediatric centres have recently received funding to support the delivery of chronic pain management programs, with funds being directed to complimentary allied health positions to create multidisciplinary teams¹¹. Key positions have been established to address patients’ physical rehabilitation (Physiotherapy, Occupational Therapy); psycho-social needs (Social Work, Psychology), Primary Care and Care Coordination (Nurse Practitioners) and ongoing administrative costs (Data Analysis and Project Management) have been funded to ensure performance management and program development. Existing adult chronic pain management programs can also be strengthened to provide rehabilitation, psycho-social and primary care support, increasing access to the EDS population, closer to home.

Section 3 – Additional Considerations: Comprehensive Care Coordination Strategy for EDS Patients

3.0 Potential Model of Care for Ongoing EDS Management

As the EDS Expert Panel reviewed the challenges and explored opportunities to provide improved care for patients with EDS, a recurring theme emerged regarding the needs for ongoing management of patients. The literature suggests that the prevalence is approximately 1:5000; however, at a recent EDS conference in Toronto, the prevalence was suggested to be 1:200. Geneticist members from the Panel shared anecdotally that requests for evaluation for EDS are increasing. For those patients with a confirmed diagnosis, geneticists frequently serve as a care coordination function for these rare disease patients given their understanding of the condition and established network. The panel also learned that pain management programs frequently serve as an initial gateway for assessment of patients with EDS. Patients and their families recount numerous encounters at various emergency departments, primary care providers, and specialists hoping to find providers with enough knowledge of their disease to provide a diagnosis and coordinate a treatment plan. Scans of other jurisdictions found that EDS patients are managed by various providers, either in a decentralized model with the patient's primary care provider coordinating specialist consultations¹², or by a geneticist and genetics counsellor providing referrals and care co-ordination¹³.

The EDS Expert Panel proposes that dedicated primary care health human resources be allocated to provide care coordination specifically for EDS patients, and to provide education to all providers caring for EDS patients in the community. Given the size of the patient population, it is recommended that two sites be established – one pediatric and one adult – comprised of a nurse practitioner and a pediatrician/family physician coordinator at each site. These professionals would:

- Manage the ongoing care of the EDS patient, either as the most responsible physician or by providing advice to a primary care provider on treatment and management of the patient in the community (in person or via telemedicine)
- Provide education to EDS patients and their families regarding the management of the condition, including pregnancy
- Provide assessments and referrals to medical, surgical and allied health care providers, as appropriate
- Follow-up with providers and patients regarding specialist consultations, provide ongoing management, as required
- Connecting EDS patients with peer-support through local EDS agencies
- Maintain a voluntary registry of EDS patients for the purposes of understanding the patient population (given the condition's suspected under-diagnosis) and, for future research purposes
- Provide EDS-specific educational support to primary care and specialist physicians in community and hospital settings, leveraging established programs where possible such as Project ECHO for chronic pain¹⁴

Section 4 – EDS Expert Panel Recommendations

4.0 Action Items

The main objective of the EDS Expert Panel was to explore barriers to access for neurosurgery EDS patients. During research and deliberations, the EDS Expert Panel determined that, given that it is a rare disease, the patient population in Ontario is small. Though comprehensive data was limited, anecdotally, the EDS Expert Panel agreed that episodes among this population indicating neurosurgical intervention are infrequent. Patients report a lack of understanding of the condition among health care providers, and resulting frustration in seeking remedial care for ongoing symptoms. Given these factors, the EDS Expert Panel agreed it would be important to clarify criteria for when neurosurgical referral is required, what diagnostic investigations are needed and indications for neurosurgical intervention. Presented as part of this Report, this information will require further dissemination to Ontario's Medical Community.

Action Item: *CCSO to develop a brief background on Ehlers-Danlos Syndrome and share referral criteria with Ontario's Medical Community.*

4.1 Recommendations

Neurosurgical Capacity Considerations

Since the EDS patient population requiring neurosurgical intervention is limited, and capability to treat these patients is available in Ontario, the patient volume can be absorbed within current system capacity. However, other Canadian jurisdictions or other patient types with conditions that cause cranio-cervical instability may warrant sufficient volumes to create specialized neurosurgical programs, as discussed in Section 2.

Recommendation: *Current Ontario EDS patient volumes can be absorbed within current system capacity. Volumes of EDS patients from other jurisdictions or patients with other conditions that experience cranio-cervical instability were not assessed as part of the EDS Expert Panel's work, however, there may be merit for the MOHLTC to consider proposals for cranio-cervical fusion programming.*

Co-ordination of Care for Patients with EDS

Patients expressed tremendous frustration with the lack of knowledge of EDS among health care providers, and indicated that, in their experience, the lack of knowledge results in confusion around treatment protocols and appropriate care pathways. This experience can be generalized to other rare disease populations, who, as the EDS Expert Panel learned, tend to rely on geneticists to assist with system navigation and referrals. As a consultative service, genetic clinics are not in a position to support the ongoing care co-ordination and management of this patient population, which appears to be increasing in genetic evaluation referral.

Recommendation: *Centralized primary care co-ordination (both in paediatric and adult settings) with expertise in the management and treatment of EDS patients should be considered. Further quantification and confirmation of the patient volumes is required. Some data was collected through the Expert Panel members (from geneticists and pain management providers) however; a fulsome data collection effort will be needed to appreciate the volumes and demographics of the population requiring co-ordination.*

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- ⁷ The ILC Foundation is an Ontario-based, registered charity focused on Improving the Lives of Children and families living with Chronic Pain. Many people with EDS live with chronic pain.
- ⁸ The ILC Foundation (2015, November 6). Chronic Pain Impact On Difficult to Diagnose Diseases Ruling Out Ehlers-Danlos Syndrome (EDS), 10.
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- ¹¹ Ministry of Health and Long-Term Care (2015, March 6) Expanding Access for Chronic Pain Treatment to Children, <http://news.ontario.ca/mohltc/en/2015/03/expanding-access-to-chronic-pain-treatment-for-children.html>
- ¹² Decentralized models are practiced in the National Health Service, UK and at the Mayo Clinic, US
- ¹³ Geneticist led models are practiced at Centre for Medical Genetics – Gent, Belgium; Greater Baltimore Medical Centre, US
- ¹³ Project ECHO uses the Ontario Telemedicine Network to link primary care providers to educate primary health care providers on how to manage chronic pain safely and effectively in the community.

Appendix A – Ehlers-Danlos Syndrome Expert Panel Members

Co-chairs:

- Dr. James T. Rutka, Paediatric Neurosurgery, SickKids
- Karen Kinnear, Vice President, Clinical, SickKids

Members:

- Dr. Fiona Campbell, Anesthesia and Pain Management, SickKids
- Dr. Hannaneh (Hanna) Faghfoury, Clinical and Metabolic Genetics, University Health Network
- Dr. Michael Fehlings, Adult Neurosurgery – Spine, University Health Network
- Dr. Thomas Forbes, Adult Vascular Surgery, University Health Network
- Dr. Allan Gordon, Neurology and Pain, Sinai Health Systems
- Dr. Juan Guzman, Internist, Syncope and Autonomic Disorders, McMaster
- Dr. Andrew Howard, Paediatric Orthopaedic Surgery, SickKids
- Linda Kostrzewa, Director, Critical Care Services Ontario
- Dr. Bernard Lawless, Provincial Lead – Critical Care Services Ontario
- Dr. Roberto Mendoza, Clinical and Metabolic Genetics, SickKids
- Dr. Garry Salisbury, Senior Medical Advisor – Ministry of Health and Long-Term Care
- Jennifer Tyrrell, Nursing – Pain Management/EDS, SickKids

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