Missed medical diagnosis in CHARGE syndrome

POTS, Migraine Cyclical vomiting and more

CHARGE Syndrom e.V.

Oberwesel
Germany 2022

Dr. Kim Blake, Professor of Pediatrics
Dalhousie University, Nova Scotia, Canada
kblake@dal.ca
www.drkimblake.com

DALHOUSIE UNIVERSITY

IWK Health Centre

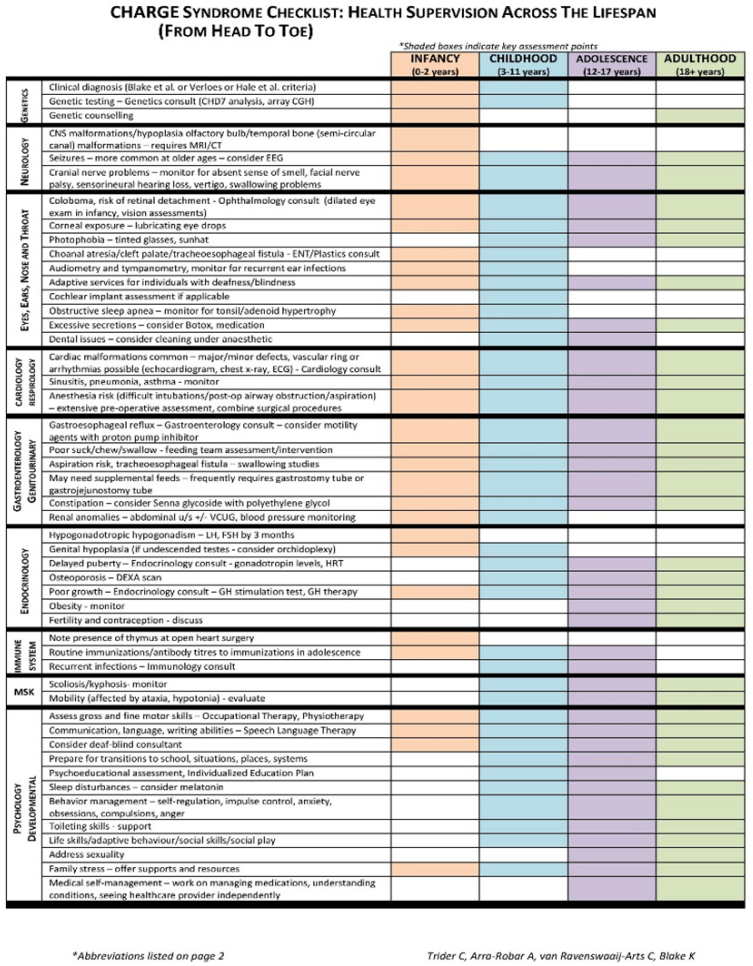
Flying again to conferences

Halifax from the air

Trick or Treat from the IWK hospital

Objectives

- To make you aware of Postural Orthostatic Tachycardia Syndrome (POTS) and its treatments.
- To help you understand migraine, cyclical vomiting and their connection to CHARGE syndrome.
- To explain and expand the use of the CHARGE syndrome checklist.



CHARGE Syndrome Checklist: Health Supervision Across The Lifespan (From Head To Toe)

*Shaded boxes indicate key assessment points

		INFANCY (0-2 years)	CHILDHOOD (3-11 years)	ADOLESCENCE (12-17 years)	ADULTHOOD (18+ years)
Genetics	Clinical diagnosis (Blake et al. or Verloes or Hale et al. criteria)				
	Genetic testing – Genetics consult (CHD7 analysis, array CGH)				
	Genetic counselling				
Neurology	CNS malformations/hypoplasia olfactory bulb/temporal bone (semi-circular canal) malformations – requires MRI/CT				
	Seizures – more common at older ages – consider EEG				
	Cranial nerve problems – monitor for absent sense of smell, facial nerve palsy, sensorineural hearing loss, vertigo, swallowing problems				
Eyes, Ears, Nose and Throat	Coloboma, risk of retinal detachment - Ophthalmology consult (dilated eye exam in infancy, vision assessments)				
	Corneal exposure – lubricating eye drops				
	Photophobia – tinted glasses, sunhat				
	Choanal atresia/cleft palate/tracheoesophageal fistula - ENT/Plastics consult				
	Audiometry and tympanometry, monitor for recurrent ear infections				
	Adaptive services for individuals with deafness/blindness				
	Cochlear implant assessment if applicable				
	Obstructive sleep apnea – monitor for tonsil/adenoid hypertrophy				
	Excessive secretions – consider Botox, medication				
	Dental issues – consider cleaning under anaesthetic				
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*Abbreviations listed on page 2

Trider C, Arra-Robar A, van Ravenswaaij-Arts C, Blake K

Have the checklist available for later in the presentation

Case report

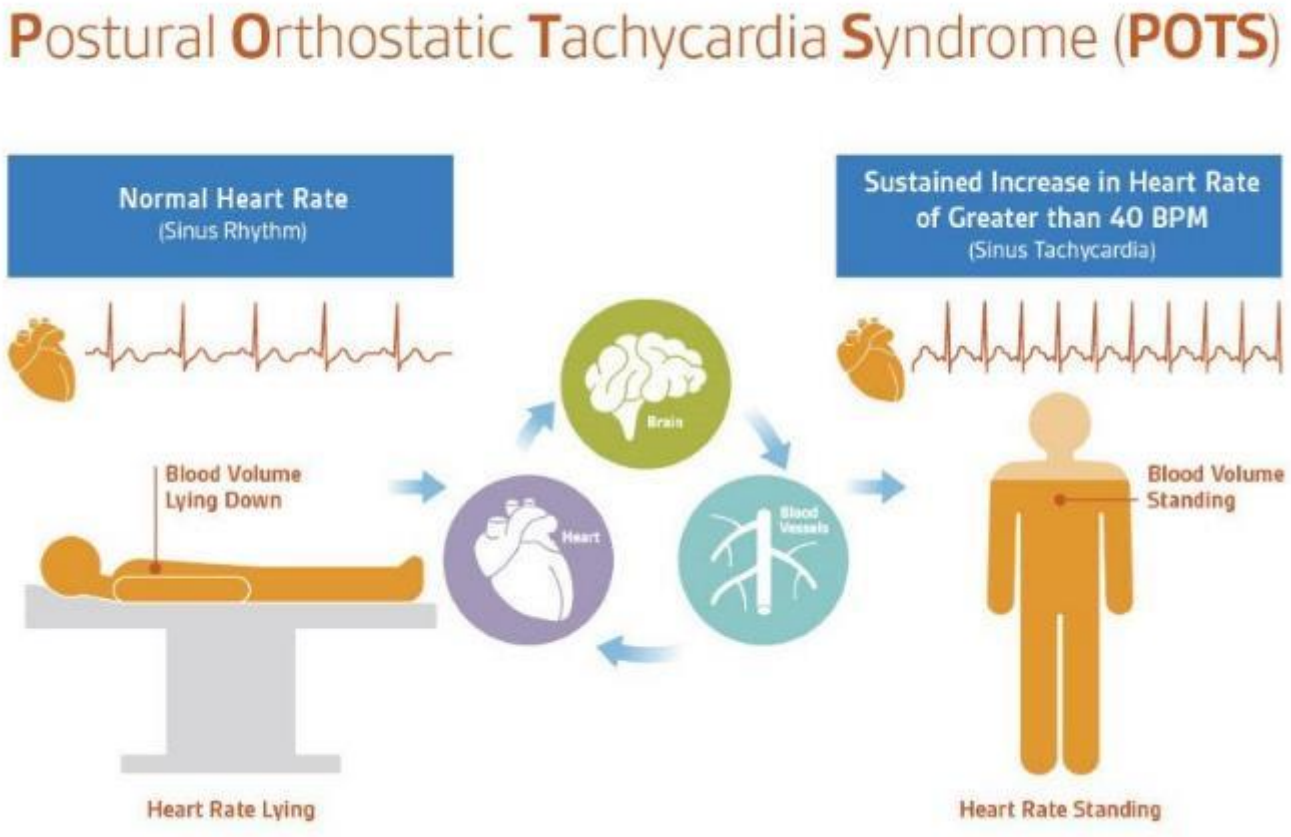
A 17-year-old female with CHARGE Syndrome was seen in the CHARGE Clinic at the IWK with symptoms suggestive of POTS. These included:

- Physical fatigue on hot days over the last year
- Heart rate that at times elevated to 140 bpm
- Agitation and discomfort when moving from a lying to standing position
- Many events of vomiting, loss of colour in the face, sweatiness, pre-syncope and diarrhea following standing up.
- One instance severe enough that prompted a visit to the Emergency Department and admission overnight.

What is POTS?

- “POTS” stands for Postural Orthostatic Tachycardia Syndrome
  - Postural = position of your body
  - Orthostatic = standing upright
  - Tachycardia = very fast heart rate
- It is a clinical syndrome that falls under the umbrella of dysautonomic conditions
  - This means that the symptoms arise from dysregulation of the autonomic nervous system

Why does POTS happen? (Physiology)



- POTS is characterized by a rapid increase in heart rate upon standing. Symptoms are often relieved by lying down.
- Vasodilatation in the lower limbs (blue color) not enough blood goes to head and neck. Resulting in increased heart rate.

How to diagnose POTS with a Tilt Table Test

Heart rate and blood pressure were recorded throughout the test. The blood pressure did not change, but the heart rate increased by over 40 beats per minute (76 → goes to 120) when she was positioned to 90° (upright) Lowering her to a supine position returned the heart rate to normal.

Study: Postural Orthostatic Tachycardia Syndrome (POTS) in CHARGE syndrome

Julia Morrison, George Williams, Angela Arra, Kim Blake

METHODS: The COMPASS 31, a validated questionnaire designed to measure dysautonomic symptoms, was adapted for this study. Data from individuals with CS age 12 or older (not just those with dysautonomic symptoms). The questionnaire listed symptoms (e.g., tachycardia, presyncope, fatigue, nausea, constipation) with a Likert scale from 1 (occurs never) to 4 (occurs often, e.g., once per week)

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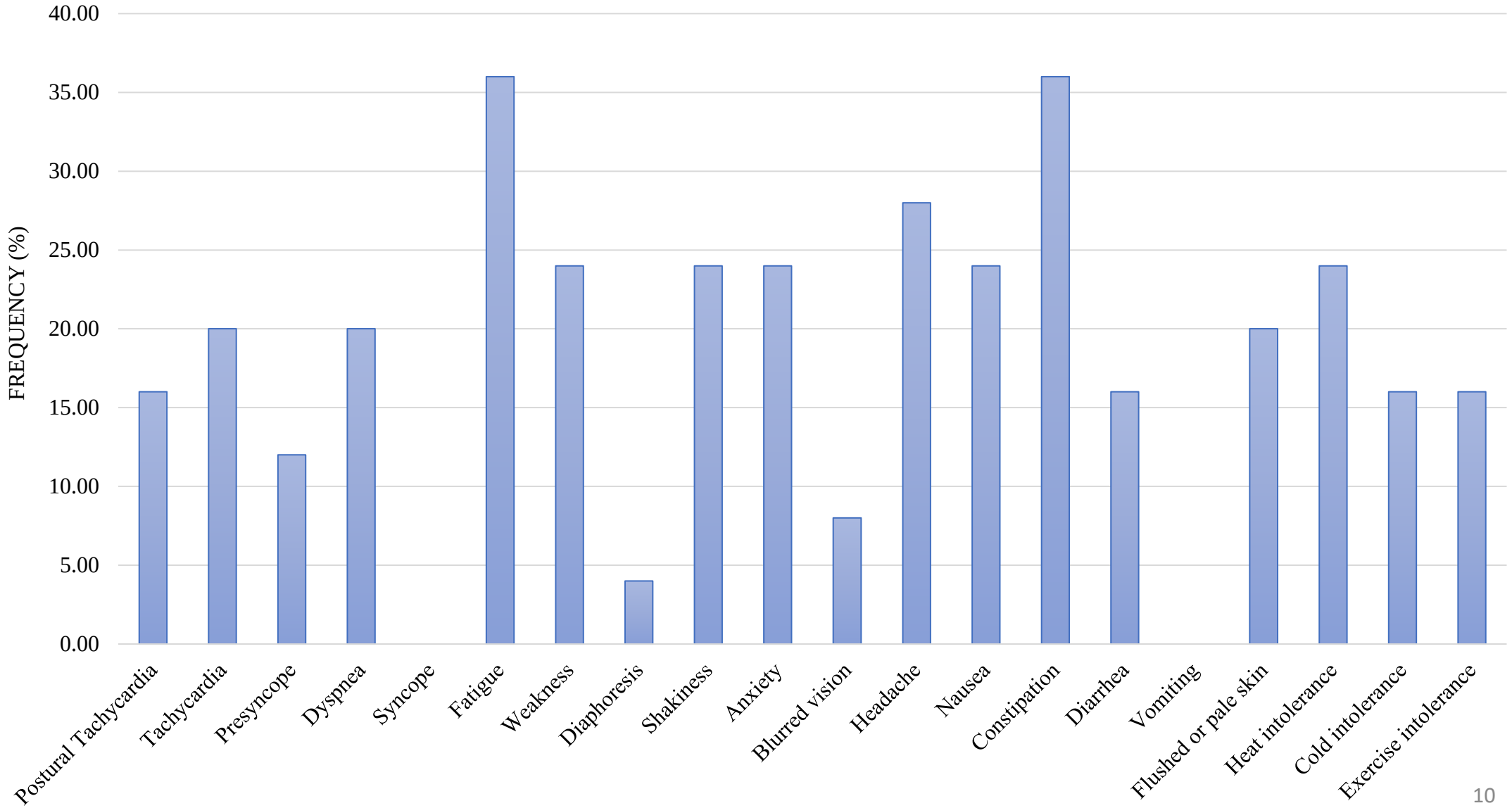
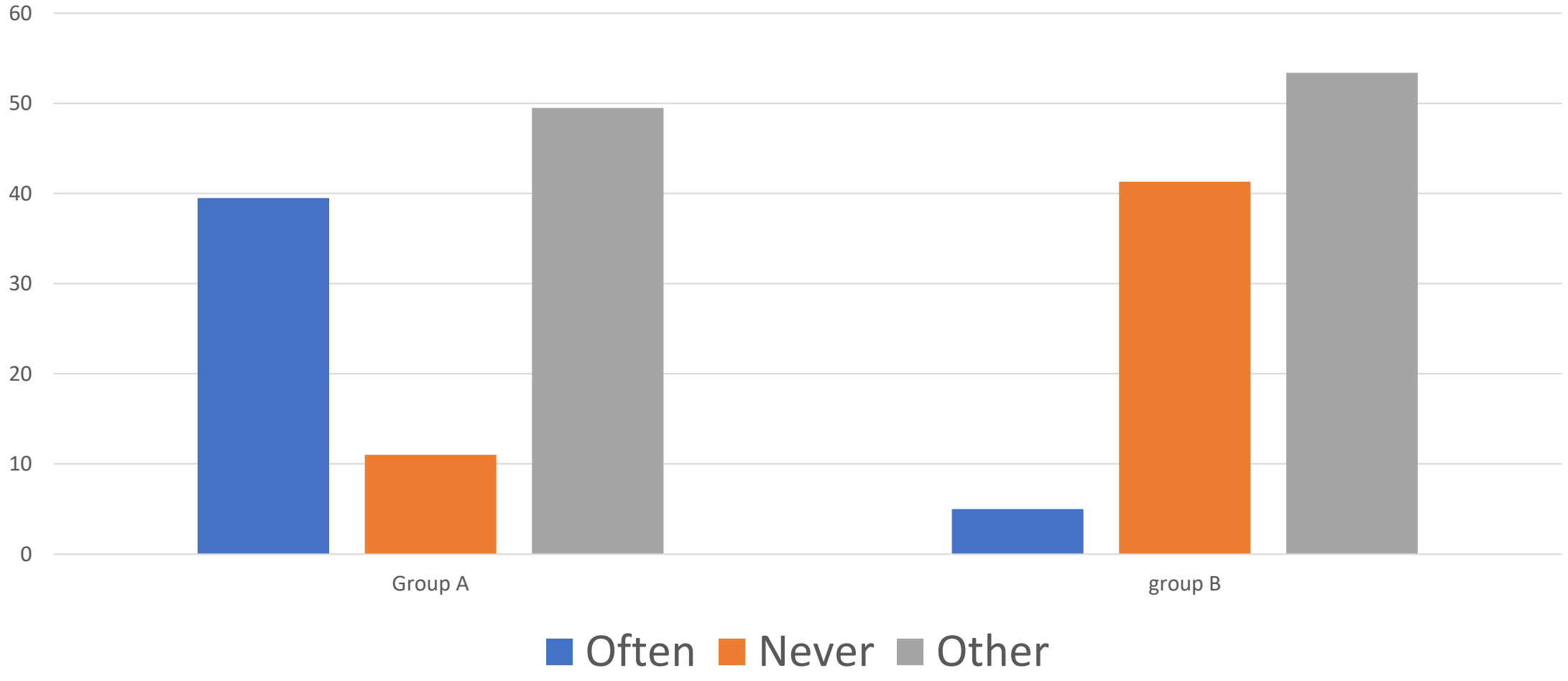
Results

- 25 (F=20, M=5) participants, age range of 12 to 33 (mean 21.5) years.
- Tachycardia, headache, fatigue and constipation (frequency 20-36%).
- The mean number of symptoms occurring **“often”** (ranked 4) was 3.75.
- Responses were stratified into two groups based on this mean. In the “above average” group, (n=10) POTS symptoms occurred with a high frequency (e.g., at least once per week) in 39.5% of participants. In the “below average” group (n=15), symptoms were reported with a high frequency just 5% of the time.

Frequency of Symptoms on a weekly basis



Average percentage of participants in each group who experienced symptoms “often” (weekly) vs. “never”



Group A = above average POTS Symptoms (n=10)

Group B = below average POTS Symptoms (n=15)

In their own words

"…At this point we were using a wheel-chair every time we went to the store because she was so fatigued just from walking to the car to the inside of the store and was getting dizzy."

- "It's awful & we have to go to the hospital regularly for fluids to help her come out of the episodes. She can't walk, talk, eat, or drink & feels like she's falling even when she is laying down. She misses 2-3 days of school a week & sleeps most of the time she is there."

Discussion from our research

- POTS may be more frequently found in older individuals with CS and should alert families and practitioners to consider this when an individual with CS presents with fatigue and dizziness especially when triggered by heat and stress.
- 10-minute stand test can be used in an office setting or at home.
- Dysautonomia; problems with the autonomic nervous system, (ANS) is likely in CHARGE syndrome given the temperature and pain variability.

Postural Orthostatic Tachycardia Syndrome (POTS)

Just like CHARGE syndrome POTS can affect most systems of the body

Symptoms and signs:

- Brain fog (lightheaded ness)
- Fainting
- Heart palpitations
- Fatigue

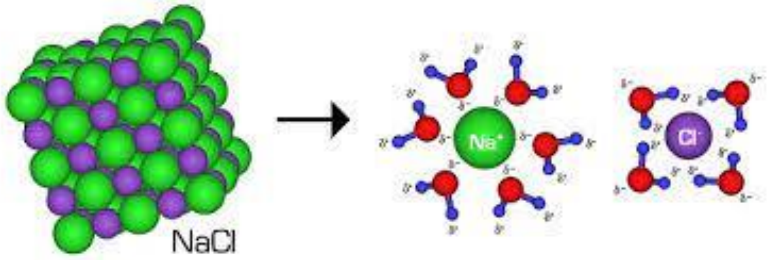
CHARGE conference 2019

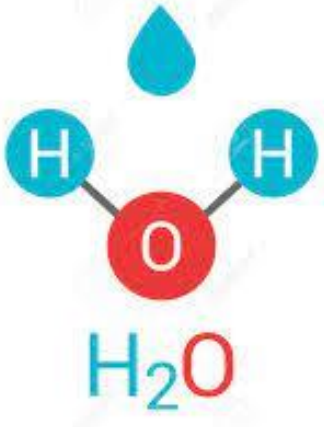
Abdominal Symptoms:

- Vomiting
- Nausea
- Diarrhea
- Bloating
- Constipation
- Cramping

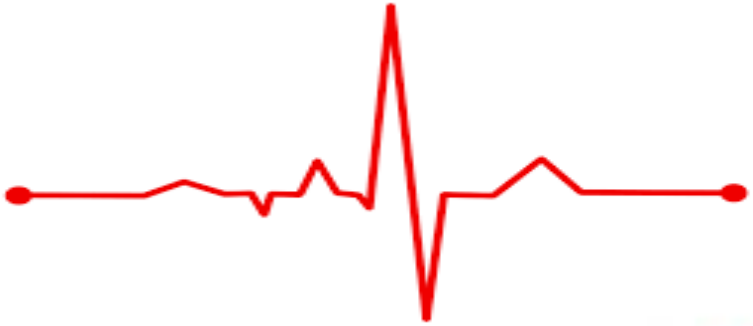
Treatments – Nonpharmacological

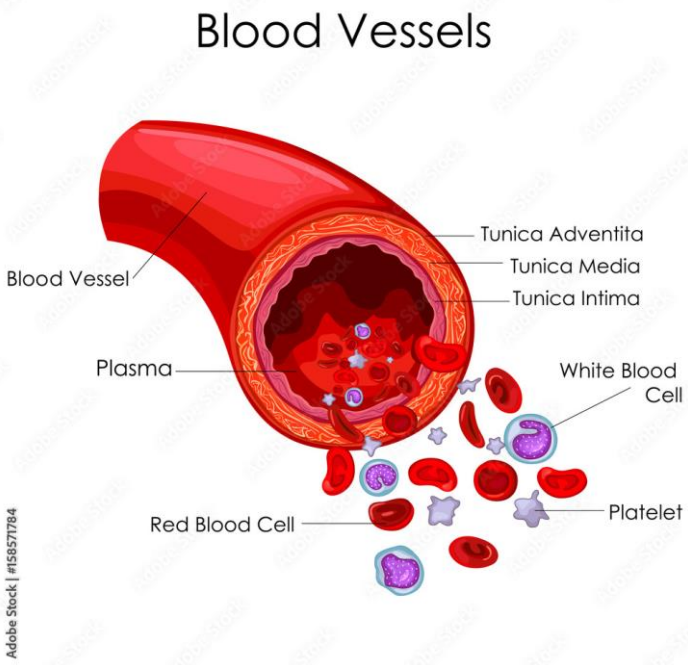
- Watch for triggers e.g., hot weather,
- Fluids with electrolytes and Increase salt in diet
- Avoid prolonged standing
- Limit caffeinated drinks
- Small frequent meals and lower carbohydrates.
- Compression stockings
- Refer to rehabilitation specialists
- Aquatic Therapy for PT – range of motion
- Physical therapy – “build up” conditioning of exercise

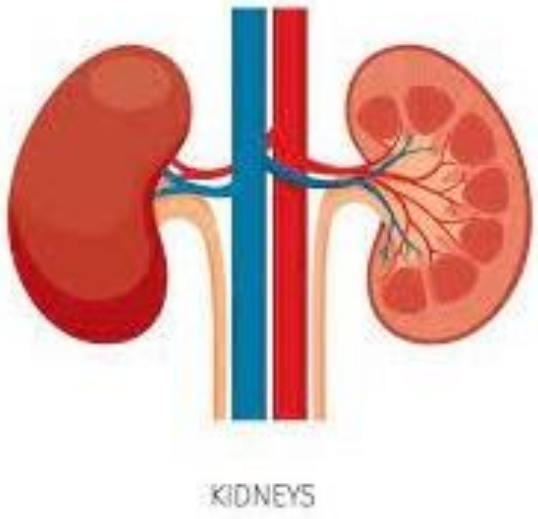




Treatments - Pharmacological

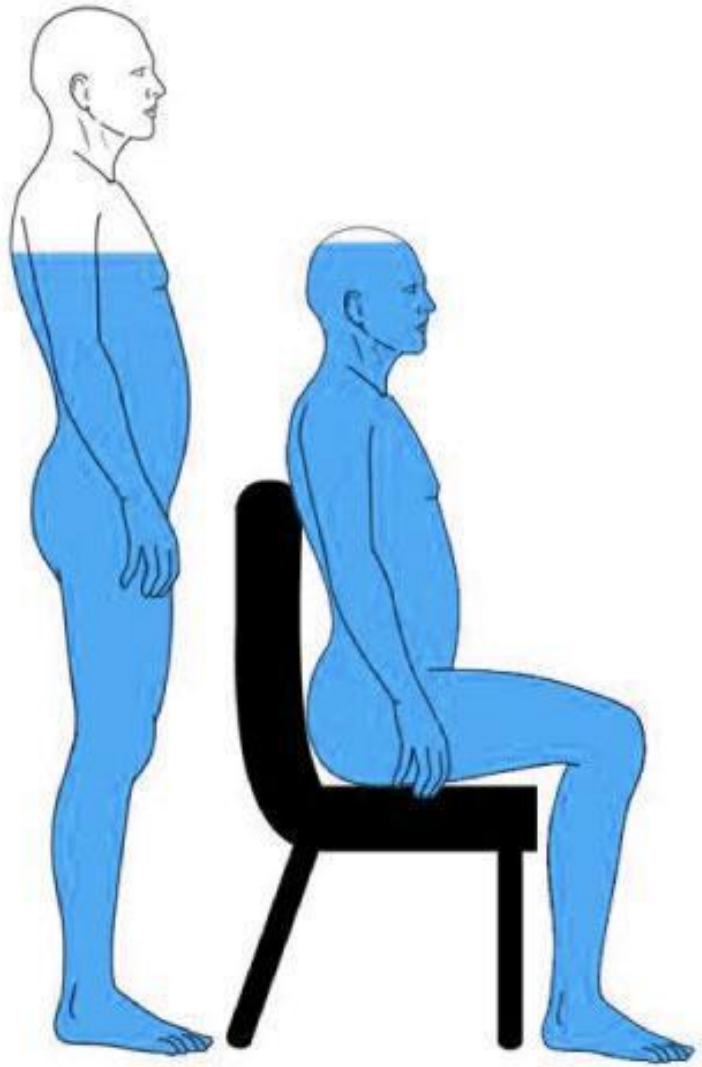






- Fludrocortisone. Helps the kidneys retain sodium (to treat Syncope and hypovolemia)
- Beta-Blockers Helps to block effort of adrenal hormone on lowest heart rate. (use low dose for palpitation).
- Pyridostigmine particularly for constipation.
- Midodrine – improving blood vessel constriction.
- Refer to neurology and or Cardiology.

Postural Orthostatic Tachycardia Syndrome



Symptoms

Dizziness

Sweating

Fatigue

Shortness of Breath

Chest Pains & Heart Palpitations

How To Treat It

Eat Smaller Meals & Fewer Carbohydrates

Increase Fluid Intake

Avoid Caffeine

Increase Salt Intake

Avoid Prolonged Standing

Summary and Recommendations

POTS is difficult to diagnose – especially with individuals who have multi-sensory impairment

There is likely more overlap with CHARGE syndrome than we currently understand

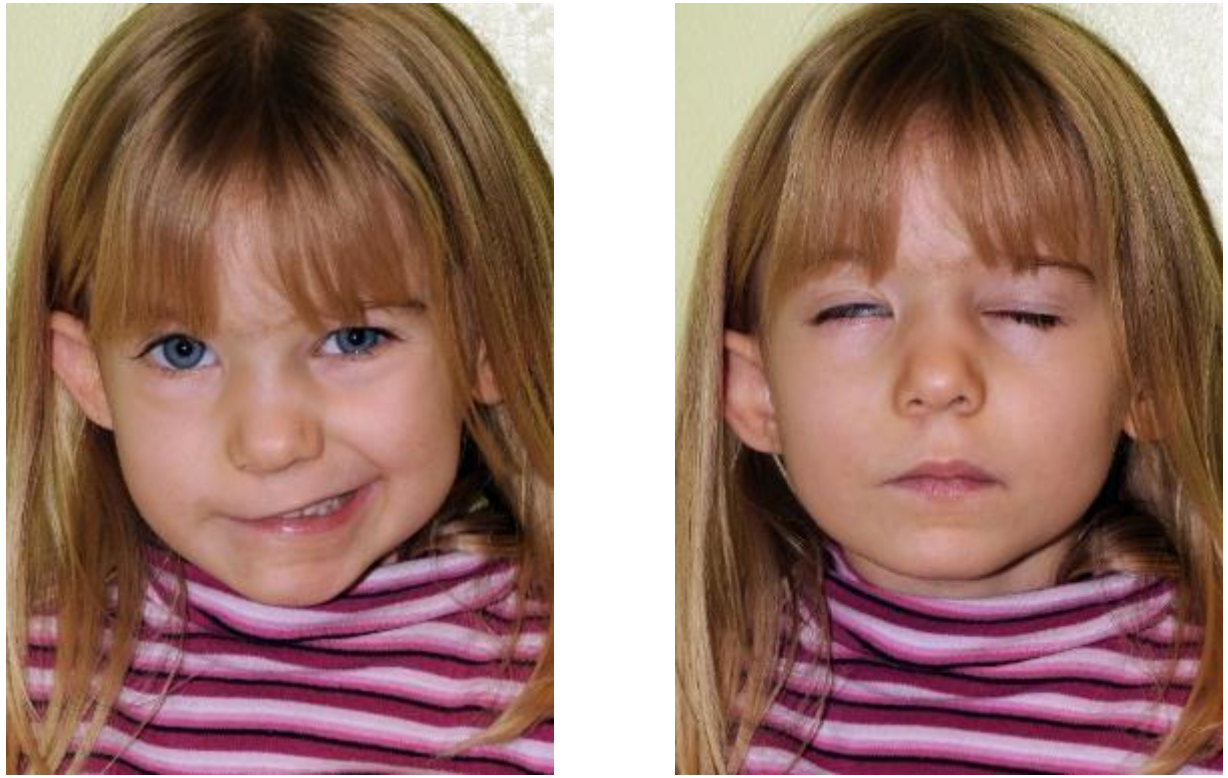
Awareness of the condition and associated triggers. Monitoring fluid and salt intake, exercise and conditioning and taking breaks during periods of activity

Migraines in CHARGE Syndrome

- Can be an atypical presentation in CHARGE syndrome
- Look for family history and triggers.
- “Abdominal migraine” in younger individual can progress to typical migraine

An individual with CHARGE syndrome – presenting with decreased sensitivity of the cornea

- Admitted with diarrhea and vomiting.
- Abnormal ears and facial palsy.
- “Sand not felt in her eyes”.
- CHD7 anomalies, diagnosed with CHARGE Syndrome with few clinical features.
- Started to get migraines at age 4 years
- Migraines so severe she would miss school, need to wear sunglasses at all times, nausea and vomiting.



Showing Right facial palsy and Hypoalgesia (Cranial Nerve VII and V)

A case report of Migraine Treatment in CHARGE syndrome using Onabotulinum Toxin A .

Morrison, Fisher, Arra, Bezuhly, Blake

- MT was getting bullied regarding her facial palsy and received injections of Botox® into the left lower lip muscle (normal side) to relax the face for more symmetry
- Coincidentally, this relieved her previously treatment-resistant chronic migraine headaches
- lower lip muscle injections are not typical for Botox in migraine management

www.drkimblake.com

Method of Botox treatment

- Botox treatment to normal facial nerve. Every 3-4 months. Tracking improvement by diary of migraines.
- Possibly practice-changing approach to migraine treatment for children, specially those with CHARGE and/or facial nerve palsies

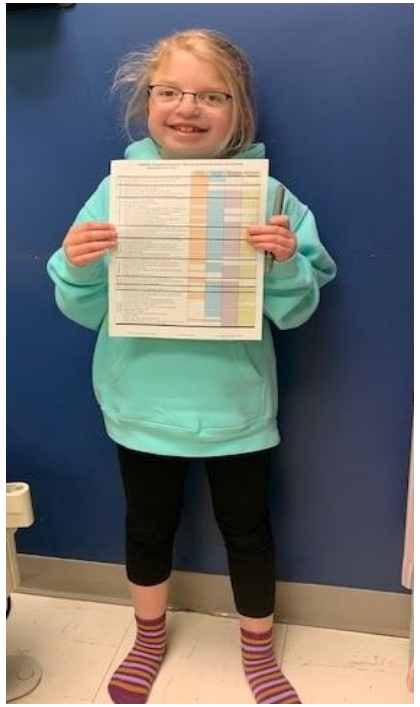
Migraines – Evaluation and treatment

- Communication challenges
- Atypical presentation of the migraines
- Suggest using Pain Scale and looking for triggers.
- Medical prophylactics treatment – daily vitamin D 1000-2000 units, Magnesium and riboflavin.

Cyclical Vomiting

Four phases

- Normal
- Prodrome – odd feelings
- Vomiting
- Recovery
- Often a history of migraines.



Case history of cyclical vomiting

"CV is rare, CHARGE is rare – don't chalk everything up to its just CHARGE"

- 4-year-old girl with vomiting every 1-2 months for 3-6 days.
- Morning stomach cramping not revealed by anything – venting g-tube, meds – lead to vomiting.
- Family history of sever migraines.
- Investigations normal and no treatment helped.
- Triggers were sleep problems, stress and some additives in junk food.
- Similar management to migraines. Try low fat, more meals with L-Carnatine and Co-enzymes Q10.
- Drugs that can be used are associated with Amitriptyline (or other anti depressants) Valproate, Topiramate, Gabapentin and

CHARGE Clinical checklist:

Health supervision across the lifespan

- Key assessment/reassessment points across the lifespan
- Supports all care providers to manage patients with CHARGE syndrome
- Families can use this and bring it to their doctors' appointments.

CHARGE SYNDROME CHECKLIST: HEALTH SUPERVISION ACROSS THE LIFESPAN (FROM HEAD TO TOE)

**Shaded boxes indicate key assessment points*

		INFANCY (0-2 years)	CHILDHOOD (3-11 years)	ADOLESCENCE (12-17 years)	ADULTHOOD (18+ years)
GENETICS	Clinical diagnosis (Blake et al. or Verloes or Hale et al. criteria)				
	Genetic testing – Genetics consult (CHD7 analysis, array CGH)				
	Genetic counselling				
NEUROLOGY	CNS malformations/hypoplasia olfactory bulb/temporal bone (semi-circular canal) malformations – requires MRI/CT				
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	Corneal exposure – lubricating eye drops				
	Photophobia – tinted glasses, sunhat				
	Choanal atresia/cleft palate/tracheoesophageal fistula - ENT/Plastics consult				
	Audiometry and tympanometry, monitor for recurrent ear infections				
	Adaptive services for individuals with deafness/blindness				
	Cochlear implant assessment if applicable				
	Obstructive sleep apnea – monitor for tonsil/adenoid hypertrophy				
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	Dental issues – consider cleaning under anaesthetic				
CARDIOLOGY RESPIROLOGY	Cardiac malformations common – major/minor defects, vascular ring or arrhythmias possible (echocardiogram, chest x-ray, ECG) - Cardiology consult				
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GASTROENTEROLOGY GENITOURINARY	Gastroesophageal reflux – Gastroenterology consult – consider motility agents with proton pump inhibitor				
	Poor suck/chew/swallow - feeding team assessment/intervention				
	Aspiration risk, tracheoesophageal fistula – swallowing studies				
	May need supplemental feeds – frequently requires gastrostomy tube or gastrojejunostomy tube				
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	Sleep disturbances – consider melatonin				
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	Family stress – offer supports and resources				
	Medical self-management – work on managing medications, understanding conditions, seeing healthcare provider independently				

Trider et al AJMG 2017Mar;173(3): 684-691

**Abbreviations listed on page 2*

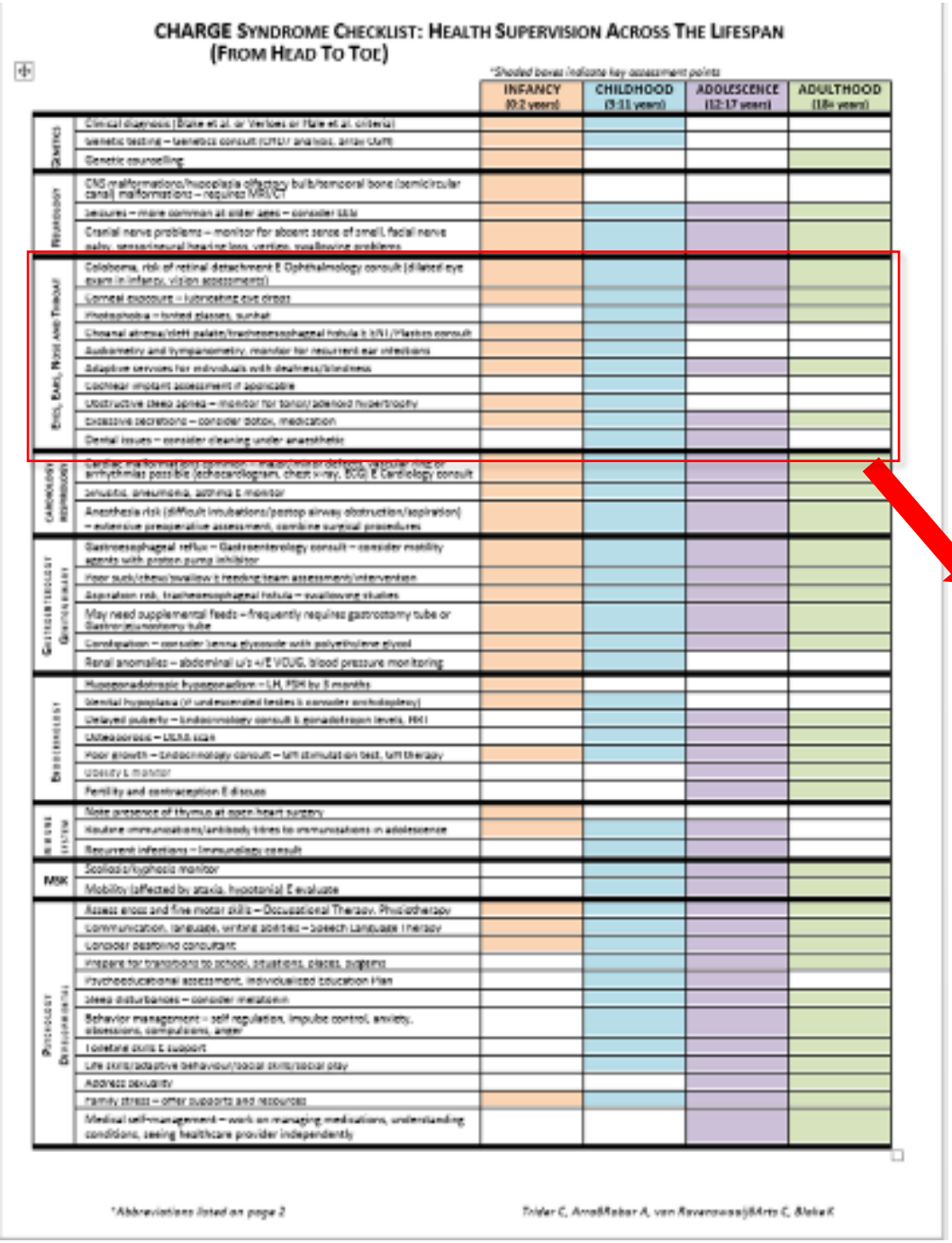
Why do we need a CHARGE **clinical** checklist?

- CHARGE syndrome is a complex multi factorial condition and a checklist can…
  - Improve care for individuals and families
  - Prevent missed diagnoses and facilitate early referral
  - Educate learners and professionals who are not familiar with CHARGE syndrome

2017 Orlando CHARGE conference

Developing a CHARGE Syndrome Checklist: Health Supervision across the lifespan

(From head to toe)



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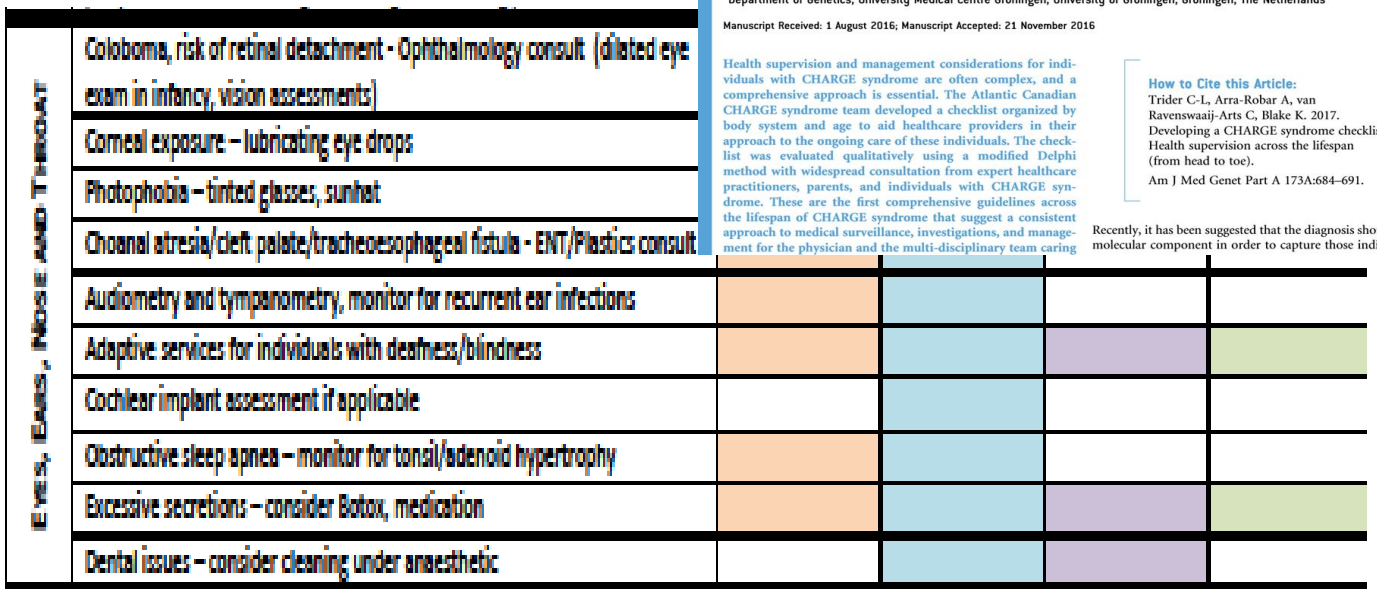

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ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Developing a CHARGE Syndrome Checklist: Health Supervision Across the Lifespan (From Head to Toe)

Carrie-Lee Trider,[1] Angela Arra-Robar,[2] Conny van Ravenswaaij-Arts,[3] and Kim Blake[2]*
[1]Department of Pediatrics, Kingston General Hospital, Queen's University, Ontario, Canada
[2]Department of Pediatrics, IWK Health Center, Dalhousie University, Nova Scotia, Canada
[3]Department of Genetics, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Manuscript Received: 1 August 2016; Manuscript Accepted: 21 November 2016

Health supervision and management considerations for individuals with CHARGE syndrome are often complex, and a comprehensive approach is essential. The Atlantic Canadian CHARGE syndrome team developed a checklist organized by body system and age to aid healthcare providers in their approach to the ongoing care of these individuals. The checklist was evaluated qualitatively using a modified Delphi method with widespread consultation from expert healthcare practitioners, parents, and individuals with CHARGE syndrome. These are the first comprehensive guidelines across the lifespan of CHARGE syndrome that suggest a consistent approach to medical surveillance, investigations, and management for the physician and the multi-disciplinary team caring

How to Cite this Article:
Trider C-L, Arra-Robar A, van Ravenswaaij-Arts C, Blake K. 2017. Developing a CHARGE syndrome checklist: Health supervision across the lifespan (from head to toe).
Am J Med Genet Part A 173A:684–691.

Recently, it has been suggested that the diagnosis should involve a molecular component in order to capture those individuals with

Trider et al AJMG 2017Mar;173(3): 684-691 . DOI:10.1002/ajmg.a.38085

How was the CHARGE syndrome clinical checklist developed

- Literature review
- Expert opinion
- Evaluated qualitatively (n=97) by a Delphi method – with Pediatricians, parents, individuals with CHARGE syndrome, deaf blind specialists, therapists =OT PT SLP endocrinologists
- Piloted by 7 multidisciplinary CHARGE syndrome clinics and medical students who had no prior knowledge of CHARGE syndrome.

Trider et al AJMG 2017

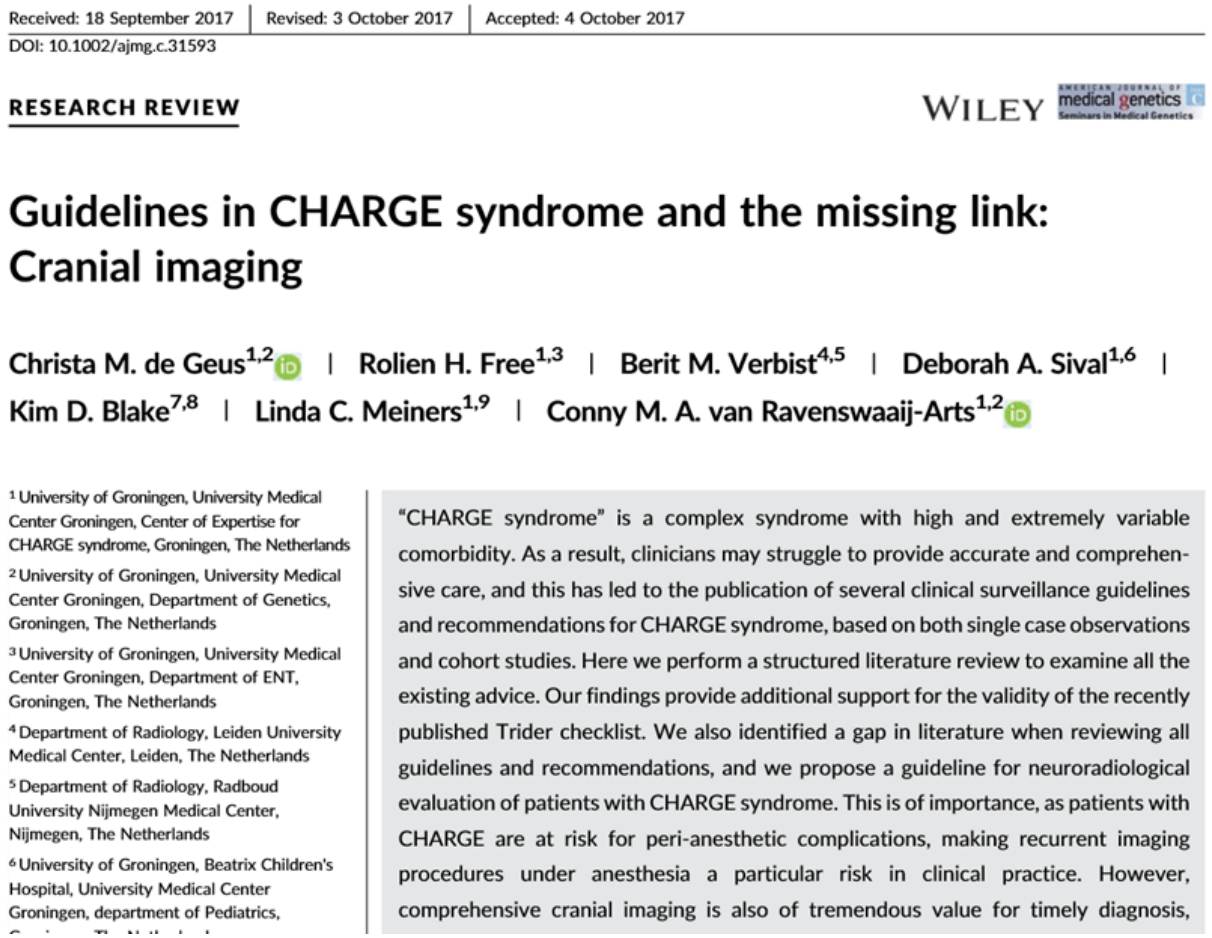
Evaluation of the checklist

Guidelines in CHARGE Syndrome and the Missing Link: Cranial Imaging

"CHARGE Syndrome clinical checklist is a well supported frame work for clinical surveillance as demonstrated by a thorough literature search"

- This is the only clinical checklist that has been validated for use with CHARGE syndrome.

- This Guidelines paper includes recommendations for cranial imagining that provide optimal care while limiting risky anesthetic procedures.



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RESEARCH REVIEW

WILEY American Journal of medical genetics Seminars in Medical Genetics

Guidelines in CHARGE syndrome and the missing link: Cranial imaging

Christa M. de Geus[1,2] | Rolien H. Free[1,3] | Berit M. Verbist[4,5] | Deborah A. Sival[1,6] | Kim D. Blake[7,8] | Linda C. Meiners[1,9] | Conny M. A. van Ravenswaaij-Arts[1,2]

[1] University of Groningen, University Medical Center Groningen, Center of Expertise for CHARGE syndrome, Groningen, The Netherlands
[2] University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands
[3] University of Groningen, University Medical Center Groningen, Department of ENT, Groningen, The Netherlands
[4] Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
[5] Department of Radiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
[6] University of Groningen, Beatrix Children's Hospital, University Medical Center Groningen, department of Pediatrics,

"CHARGE syndrome" is a complex syndrome with high and extremely variable comorbidity. As a result, clinicians may struggle to provide accurate and comprehensive care, and this has led to the publication of several clinical surveillance guidelines and recommendations for CHARGE syndrome, based on both single case observations and cohort studies. Here we perform a structured literature review to examine all the existing advice. Our findings provide additional support for the validity of the recently published Trider checklist. We also identified a gap in literature when reviewing all guidelines and recommendations, and we propose a guideline for neuroradiological evaluation of patients with CHARGE syndrome. This is of importance, as patients with CHARGE are at risk for peri-anesthetic complications, making recurrent imaging procedures under anesthesia a particular risk in clinical practice. However, comprehensive cranial imaging is also of tremendous value for timely diagnosis,

American Journal of Medical Genetics 2017

Summary of why you and your health care providers should use the CHARGE clinical checklist

- Important issues that professionals need to address at each visit-Age dependent.
- Rare health issues that can be missed in CHARGE syndrome and can lead to adverse health consequences.
- The publication can be used to support the checklist

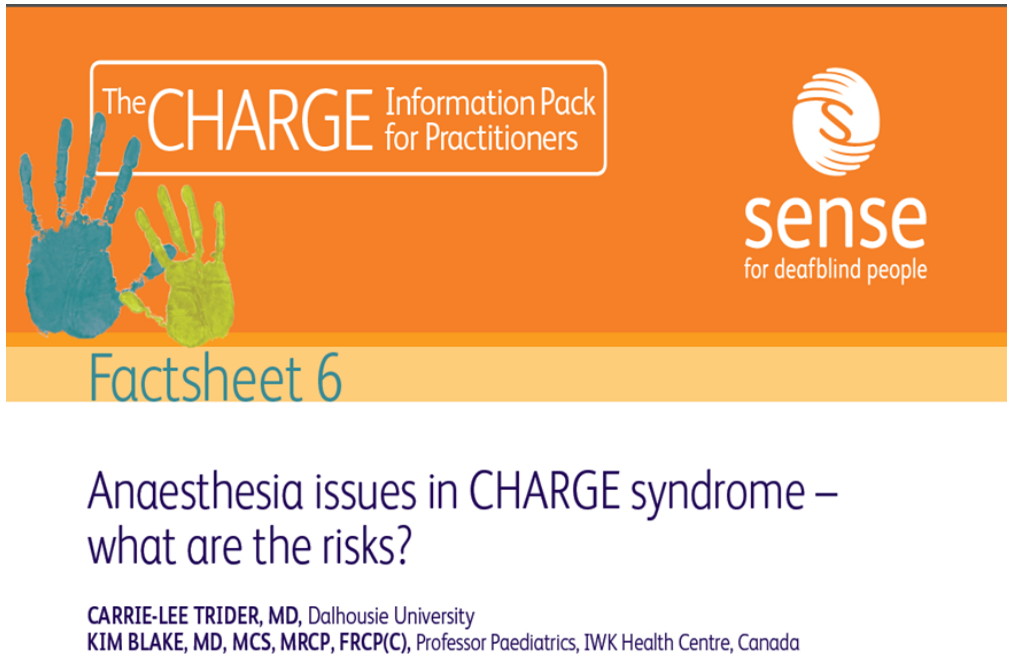
"The CHARGE Syndrome checklist is an important tool for medical students and doctors. It helps them know what questions to ask me and my mom."

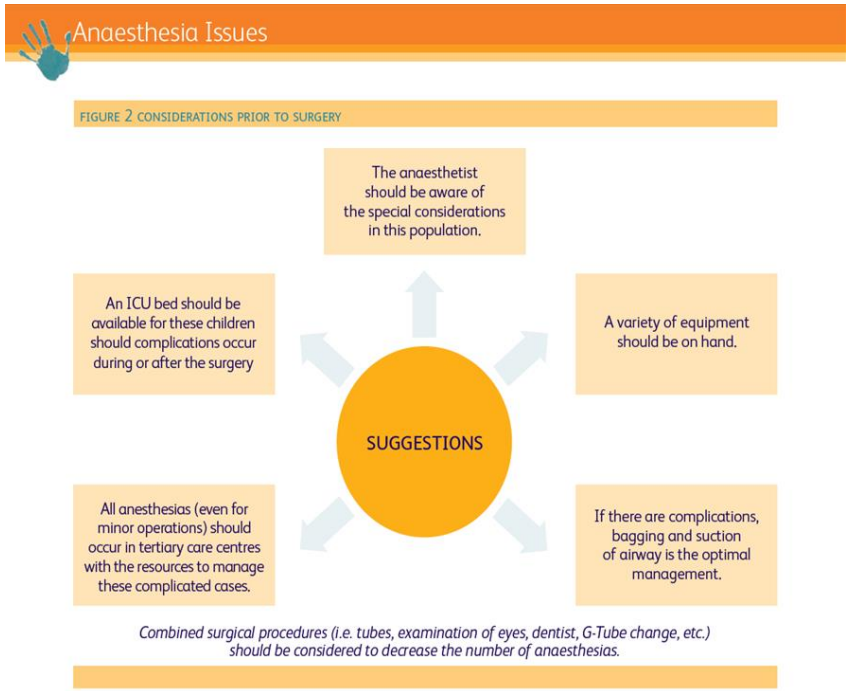
" It is nice when I go to a hospital or appointment, and someone has heard of CHARGE Syndrome before!"

Infancy (0-2 years)

Procedures requiring anesthesia should be combined where possible as there is a greater risk of anesthesia complications in individuals with CHARGE syndrome.

https://www.sense.org.uk/get-support/information-and-advice/conditions/charge-syndrome/





Childhood (3-11 years)

Gastrointestinal and feeding issues are prevalent in CS.

- We suspect that lower cranial nerve anomalies (IX, X, XI) produce abnormal gut motility and issues with the gut microbiome.

- Issues of swallowing, reflux, aspiration, abdominal pain (use the pain scale) constipation.
- Multi disciplinary team including pediatrician, gastroenterology, ENT, nutritionist, OT/PT/SL, psychologist.

ENT issues

- Obstructive sleep apnea and consider tonsillectomy and adnoidnactomy

Adolescent (12-17)

Jenna with Micaela 2021

Puberty

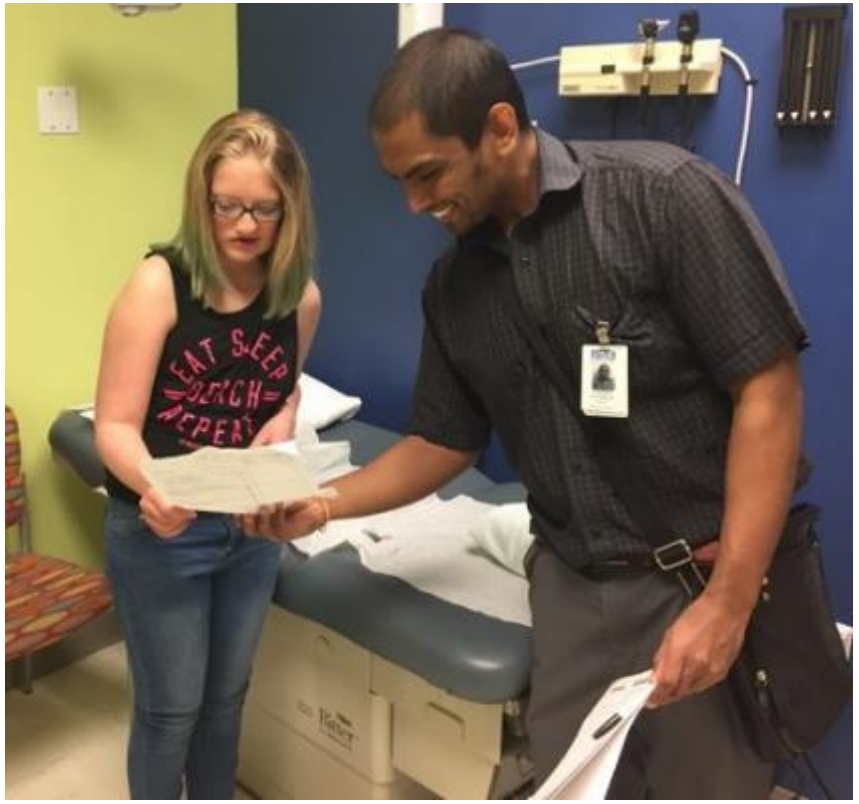
- Often delayed / disordered and requires, hormone replacement therapy.
- Referral to endocrinology around age 10.

Bone health is often forgotten

- High dose of vitamin D weight bearing exercises and HRT.

Mental Health

- *Especially Anxiety and ADHD*



2017 Medical student receiving feedback with Jenna

18 years to adulthood

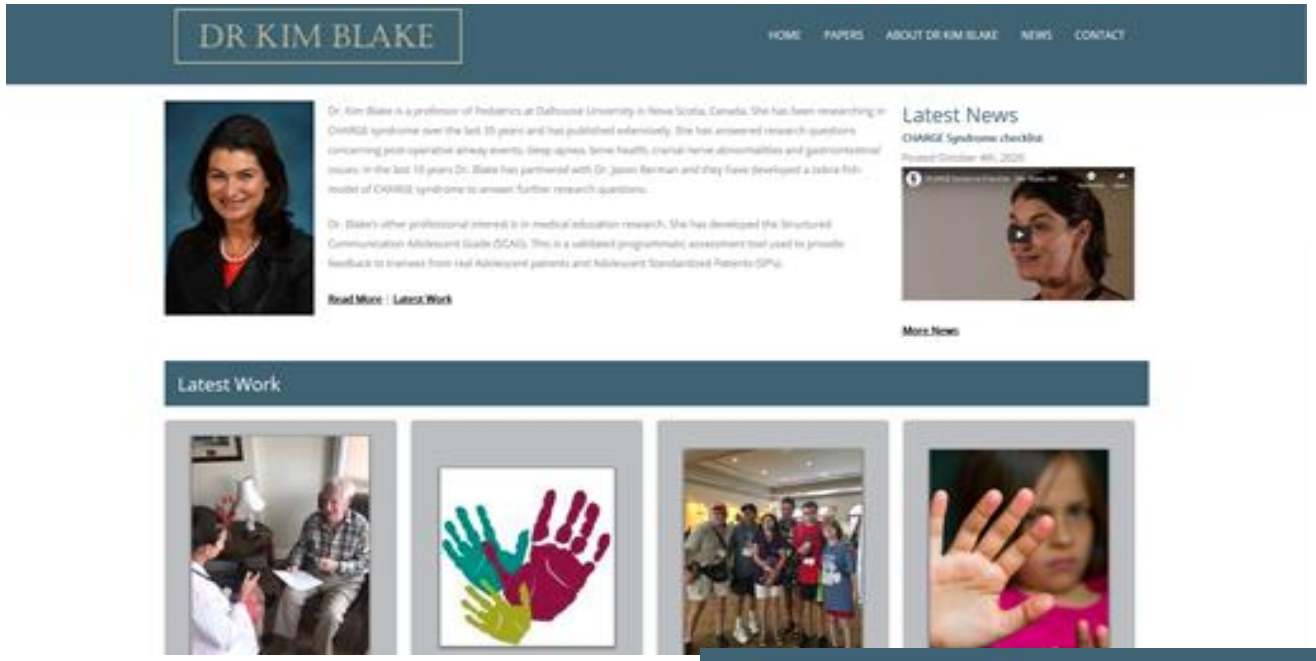
If new behavioral changes arise always consider a thorough history and physical looking for underlying medical issues.

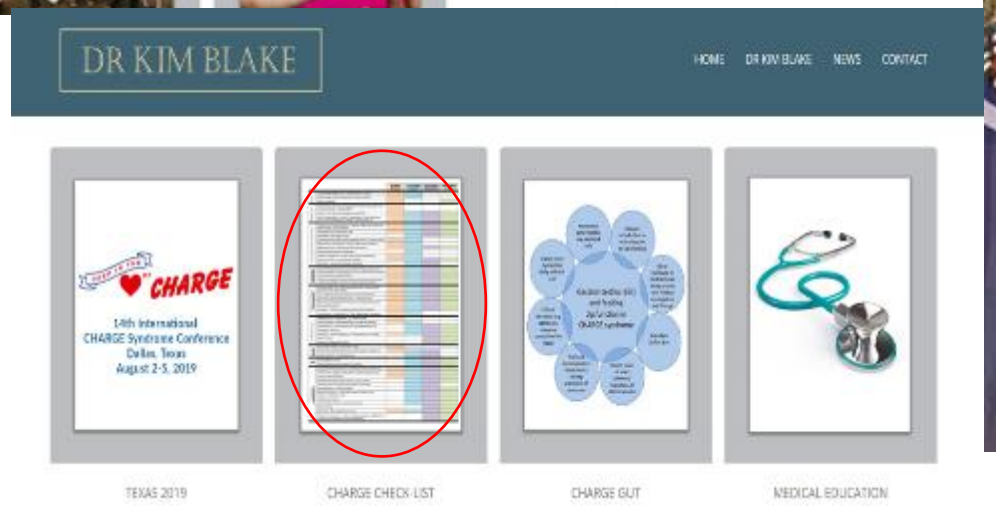
- Hearing and vision i.e. retinal detachment, wax in ears.
- Heart arrhythmias.
- Bloating and constipation.
- Migraine
- POTS (Postural orthostatic tachycardia syndrome).

Obesity is prevalent and its important to involve a nutritionist and physical/recreational therapist.

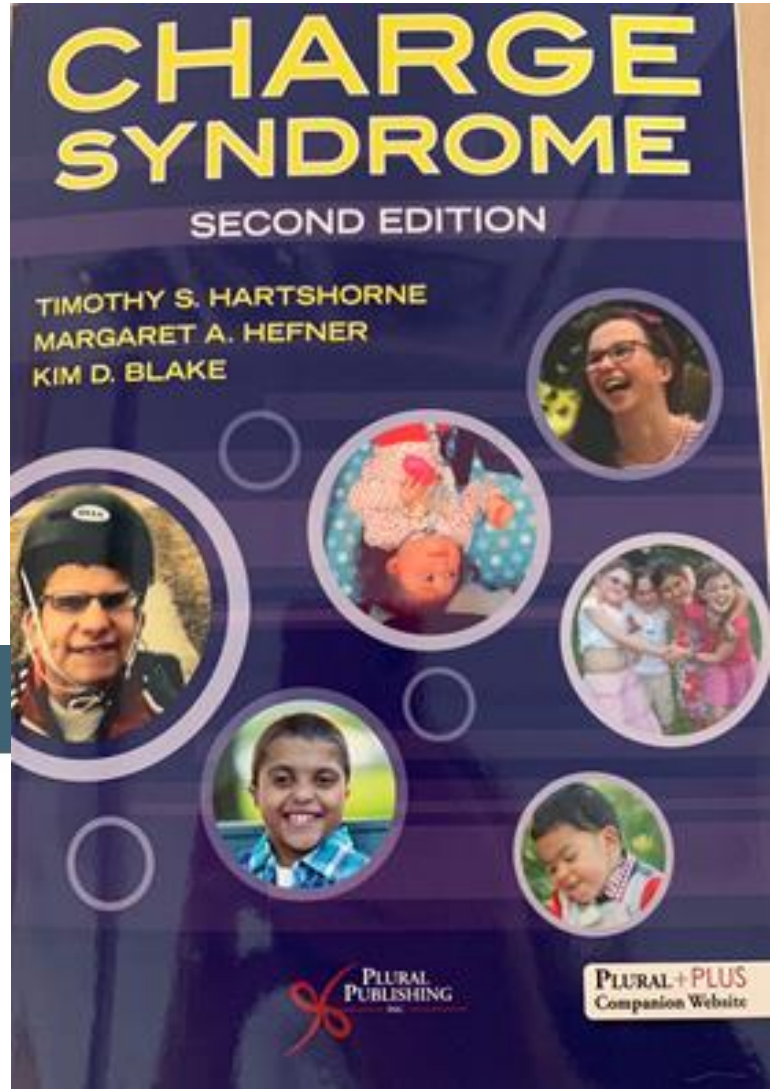
Where to locate the CHARGE clinical checklist

There is a German translated CHARGE Checklist





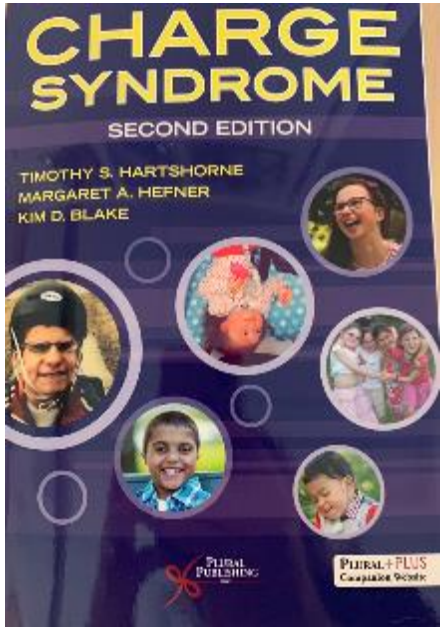
www.drkimblake.com



Knowledge translation

International Collaboration is a key to success in a rare condition.

- Website www.drkimblake.com -- a repository of Dr. Blake's research
- CHARGE Syndrome textbook second edition.
- The Atlantic Canadian CHARGE organization. Provides international consultations, problem solving, and support as individuals and families grow up with CHARGE Syndrome.



CHARGE SYNDROME AUSTRALASIA

Online course: Understanding CHARGE Syndrome

Understanding CHARGE syndrome is a 6–8-week **free** online course via an innovative training tool called MOOC (massive open online course). The course is open to anyone in the world with an interest in CHARGE syndrome:

- People living with CHARGE syndrome, their families and careers.
- Medical and nursing professionals
- Allied health professionals
- Teachers and educators
- Advocates, service delivery staff, support workers, planners

https://www.chargesyndrome.org.au/onlinecourse

Thoughts and Questions