"Guidelines in CHARGE syndrome and the missing link: Cranial imaging"

By: Christa M. de Geus, Rolien H. Free, Berit M. Verbist, Deborah A. Sival, Kim D. Blake, Linda C. Meiners, Conny M. A. van Ravenswaaij-Arts

https://doi.org/10.1002/ajmg.c.31593

AUTHORS AND THEIR CONNECTION TO THE CHARGE SYNDROME FOUNDATION:

Christa de Geus, MD (pictured with team on left and explaining research on right, above) is a physician in training to become an MD, PhD clinical geneticist. Her PhD research focuses on neurological symptoms in CHARGE syndrome (CS). She has been to multiple CS conferences as part of Dr. van Ravensawaaij-Arts' team from the Netherlands.

Rolien Free, MD, PhD, is an otolaryngologist/otologist/pediatric otolaryngologist with a particular interest in ear surgery, cochlear implantation, and speech language development in CS. She is the otolaryngologist of the CHARGE Center of Expertise in Groningen, The Netherlands.

Berit Verbist is a head and neck radiologist at the Leiden University Medical Center with a specific interest in otology (study of ears) and neurotology (nerves involved in hearing). She has published about imaging abnormalities in CS and the relevance to cochlear implantation.

Deborah Sival, MD, PhD, is a pediatric neurologist with a specific interest in fetal and neonatal developmental neurology. She is the pediatric neurologist at the CHARGE Center of Expertise.

Kim Blake, MD (pictured with two of her friends with CS in the email blast) is a developmental pediatrician at Dalhousie University Medical School and the IWK Health Centre in Halifax, Canada. She is an international expert in the area of CS and runs the Atlantic Canadian CHARGE Syndrome Clinic at IWK. Kim has mentored many individuals in CS who have gone on to do more CS research. She has presented at countless conferences and is the recipient of multiple awards (including the Star in CHARGE) and research grants from the CS Foundation. She is on the Clinical Advisory Board of the Foundation.

Linda Meiners, MD, PhD, is a pediatric neuroradiologist who has been with the CHARGE Center of Expertise in the Netherlands since 2009.

Conny van Ravenswaaij-Arts, MD, PhD (pictured above in center, with her Star, and on the left with some of her team) is a consultant in Clinical Genetics and Professor in Dysmorphology at the Department of Genetics of the University Medical Center Groningen, Netherlands, where she is also the coordinator of the CHARGE Center of Excellence. Her first US CHARGE Conference was in 2005, where she presented the discovery of *CHD7* as the CS gene. She and her colleagues and mentees have published extensively on CS. Conny is a recipient of a Star in CHARGE award and currently sits on the Scientific Advisory Board of the CS Foundation.

SUMMARY OF THE PAPER:

***Abstract*:** CHARGE is a complex syndrome that results in multiple health issues in affected individuals. Clinicians often struggle to provide accurate and comprehensive care to individuals with such a complex syndrome. There have been several clinical guidelines and recommendations for CHARGE syndrome (CS) published over the years. Some guidelines have been based on observations of a few cases and others on findings from larger cohort studies. Here we present the results of a structured review of all the existing published guidelines and advice. This review provides support for the validity of the Trider CS checklist. This search identified a gap in literature: there were no guidelines for neuroradiological (CT & MRI) evaluations of individuals with CS. We propose such guidelines here, taking into account that patients with CS are at risk for peri-anesthetic complications. Although recurrent imaging procedures under anesthesia are a particular risk in patients with CS, comprehensive cranial imaging is of tremendous value for timely diagnosis and proper treatment of symptoms and for further research. The Trider checklist and these new guidelines for neuroradiological evaluation will help clinicians provide efficient and comprehensive care for individuals with CS.

Additional summary: CS is extremely complex and can involve any organ system. Some individuals have many issues related to CS (comorbidities), others have only a few. "The clinical challenge of such a complex disorder is that some clinical problems may remain undiagnosed as other more severe or even life-threatening complications consume all medical attention." This can lead to some areas being short changed or missed all together. Thus the need for comprehensive (head-to-toe, birth-to-death) diagnosis and management guidelines. The authors begin by reviewing the Trider Health Checklist for CS (Figure 1). The next four pages are taken up by Table 1, which summarizes the recommendations for treatment or management of CS syndrome collected from the comprehensive literature review. Table 1 also notes whether the recommendations are included in the Trider checklist or not. Table 2 summarizes recommendations from literature regarding *CHD7* analysis – when it should and should not be considered. This comprises a complete summary of current recommendations for diagnosis and management of CS. They note that there are not yet published guidelines for cranial imaging in CS.

In Table 3, the authors summarize the cranial abnormalities, which are very common in CS, and note specific cranial imaging (MRI and CT specifics) that may be useful in identifying and managing each feature. The text discusses both the diagnostic value of cranial imaging and the situations in which such

imaging may be important for treatment and management. Among other things, cranial imaging can provide information about hearing impairment, surgical landmarks for cochlear implantation, and information about puberty induction (based on abnormalities of the olfactory bulb). Figure 2 shows MRIs of normal and CS clivus (part of the brain commonly different in individuals with CS).

Figure 3 is a comprehensive guideline for CT and MR imaging in CS – from background to specifics of scanning to types of abnormalities to look for. Cranial imaging and research (in humans and animal models) are further discussed in the text.

The authors conclude by noting that individuals with CS are typically followed by numerous specialists at a variety of institutions. The value of cranial imaging and the importance of coordinated care (especially to reduce recurrent anesthesia and minimize exposure to radiation) is stressed. CT involves radiation; MRI does not, but can take longer. Swaddling of infants may reduce the need for anesthesia for MRI. These radiology guidelines may enable accurate diagnostic radiologic assessment of the cranial and auditory anatomy within one session.

WHAT DOES THIS MEAN TO FAMILY/PERSON WITH CHARGE?

This is a very important paper for anyone dealing with management of medical and health issues of an individual with CS. It summarizes all of the CS management guidelines to date and adds new cranial imaging guidelines. The tables and figures summarize the information in a clear, practical format.

SHOULD I READ IT? SHOULD ONE OF MY DOCTORS READ IT?

Yes and Yes. This is one you should print out - perhaps multiple copies. Make additional copies of both **Figure 1** (Trider checklist, which can also be downloaded from the Foundation website https://www.chargesyndrome.org/wp-content/uploads/2016/03/CHARGE-Syndrome-Checklist.pdf) and **Figure 3** (cranial imaging guidelines). This paper/guidelines will be useful to the primary care physician and probably ALL of the specialists dealing with the individual with CS. The new cranial imaging guidelines will be especially helpful to the geneticist (or other doctor during the diagnostic work up), neurologist and ENT.

FULL CITATION: de Geus CM, Free RH, Verbist BM, et al. Guidelines in CHARGE syndrome and the missing link: Cranial imaging. Am J Med Genet Part C Semin Med Genet. 2017;175C:450–464. https://doi.org/10.1002/ajmg.c.31593