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BSPED Research and Innovation Award 2021 -Project Report at 24 months

Recipient - Dr Sasha Howard

Title - International Hypogonadotropic Hypogonadism Registry – I-HH: set up and development of a new rare disease registry.

Background

Hypogonadotropic hypogonadism (HH) is a severe disorder of the hypothalamic-pituitary-gonadal axis, resulting in deficiency of the reproductive hormones known as gonadotropins. Idiopathic HH, known as Kallmann Syndrome when associated with anosmia, is a rare condition affecting 1-10 per 10,000. Patients with HH have absent or significantly disordered puberty and the majority of patients have sub or infertility in adult life unless appropriately treated. Management of pubertal disorders is clinically challenging, particularly in severe gonadotropin deficiency, and the induction of spermatogenesis in males post puberty is often unsuccessful.

The I-DSD, I-CAH and I-TS registries (https://sdmregistries.org/) act as indispensable tools for monitoring clinical and patient-centred outcomes for rare diseases, including disorders of sexual development, congenital adrenal hyperplasia and, most recently, Turner syndrome. Such registries can improve clinical practice, support a wide range of primary and secondary research and act as a platform for pharmacovigilance, as they collect real world patient data within a secure, ethics-approved virtual research environment.

Accurate diagnosis of HH is often both difficult and costly. Infancy provides a window of opportunity for diagnosis, with biochemical evidence of HH during the 2nd-4th postnatal months when mini-puberty should occur. However, despite “red flags” signs in males of micropenis and/or cryptorchidism, many patients with HH do not present until adolescence, when lack of pubertal onset leads to referral. Even in adolescence diagnosis can be difficult, particularly in distinguishing this condition from isolated delayed puberty. However, accurate diagnosis is vital, both for patient well-being and for directing optimal treatment to improve health and fertility outcomes. At present, some international centres have advocated for the use of gonadotropin therapy instead of the traditional sex steroid regimes, to reproduce the mini-puberty period in infants with HH and to induce puberty in adolescents with HH, but this is not yet standard practice.

Interventional studies in rare paediatric conditions are complex and hugely costly, as the number of patients treated at each institution is small, and high-quality studies require coordination between multiple national or international centres. Electronic registries have been demonstrated to facilitate high quality observational research, as exemplified by the BSPED-endorsed I-TS study of oral versus transdermal oestradiol for induction of puberty in

Turner syndrome. While several international centres collect data on their HH patients, the I-HH will ensure this is standardised to facilitate cohort observational research into gonadotropin therapy in infants during the mini-puberty, for pubertal induction in adolescents with HH, and for maintenance therapy and outcomes in adult life.

Project Outputs

Together with colleagues from the I-DSD/I-CAH/I-TS consortium, the Endo-ERN (MTG-7) hypogonadotropic hypogonadism network, the Italian Ipoganodismo Centrale Network, and the EuRRECa Congenital HH survey group (Professor Faisal Ahmed, Jillian Bryce, Dr Marco Bonomi, Dr Supitcha Patjamontri) the core dataset for the I-HH collection tool was designed and developed. This was further reviewed and critiqued by the UK Society for Endocrinology Andrology SEN, led by Dr Channa Jayasena, with the goal of producing one electronic registry that can be used by paediatricians and adult endocrinologists alike. Moreover, input was received from European paediatric endocrinology HH specialists from Switzerland, Germany and Sweden (Dr Julia Rohayem, Dr Sabine Heger, Prof Anna Nordenstrom) to ensure that this registry will be compatible with European working practices and have good take up internationally as well as in the UK.

With the design of the I-HH data collection tool complete, the next phase of building the I-HH registry by the database team commenced. This was started once the team had completed the Turner syndrome (I-TS) module of the I-DSD registry. The database has been built and then refined in a series of iterative steps, following the model of the previous registries but with tailored features specific for HH in different age ranges and for males and females. The module is due to go live in early spring 2024. Once live, the registry will be tested by a team of experts, with review and resolution of issues arising from this testing process.

The module will be supported by a Wordpress website, and there will be 3-monthly review of progress on an ongoing basis. Data review and secondary survey of data collected will also be on an ongoing basis.

Benefit to the applicant, the home institution and how the funding has enabled advances in endocrinology/science/medicine

Rare diseases are under-represented in paediatric research. International rare disease electronic registries can improve clinical care and patient outcomes in these conditions. We have set up the I-HH registry for patients with hypogonadotropic hypogonadism, with the aim of improving outcomes for patients with this rare condition. Through patient and public interaction work, several key areas of patient care have been identified for children with HH, including accurate diagnosis, treatment of absent puberty and therapies to improve adult

fertility outcomes. The I-HH registry will address these by gathering data on current practice and supporting research to improve patient care.

The I-DSD registries have demonstrated what powerful tools international registries can be for the development of rare disease research. This I-HH project is supported by national and international expert colleagues in the field of paediatric and adult endocrinology. It is available to any centre or clinicians who care for patients with HH, and data access requesting is also open to all via the central registry. Our group, with Dr Howard as PI, will apply for data access to carry out an initial project to assess current practice in pubertal induction in patients with HH across centres. The I-HH registry will also be used to support clinical trials to identify best practice in the use of gonadotropins to induce puberty in males with HH, particularly with respect to long term outcomes such as fertility and live birth rates.