Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Improved healthcare management of children with disorders of sex development

1. Summary of the impact

Disorders of sex development (DSD) represent a broad group of rare genetic conditions (affecting 0.1–2.0% of the UK population) characterised by ambiguous external genitalia or atypical sexual development that manifests at birth or puberty, respectively. University of Glasgow researchers have established the first patient registries for DSD in the world, developed comprehensive UK clinical guidelines for DSD, worked closely with international patient support groups to raise awareness of the condition and improve the support available to those affected, and created a cutting-edge DSD clinical management network and diagnostic service for use worldwide. These innovations have improved clinical awareness of DSD and the ability to provide consistent treatment and professional support to affected individuals.

2. Underpinning research

Disorders of sex development (DSD) is an umbrella term used to describe a group of very rare genetic conditions affecting the hormone-secreting (endocrine) system in the body. These conditions are characterised by atypical external genitalia of varying severity and include androgen insensitivity syndrome (AIS; 1 in 20,000 UK births) and congenital adrenal hyperplasia (CAH; up to 1 in 18,000 UK births). DSD typically present clinically in newborns; in some instances, the condition is so complex that sex determination is near impossible, even by experts. However, DSD can also manifest in otherwise healthy young people at puberty.

A substantial body of research on DSD has been conducted at the University of Glasgow under the leadership of Prof. S Faisal Ahmed, a paediatric endocrinologist and world-leading authority on these rare conditions. Ahmed's standing in this discipline is underlined by his lead in developing clinical guidelines for DSD. For example, in 2006, he was a member of the Consensus Group that developed a guideline on behalf of two leading paediatric endocrinology societies.[1] This document was the first to address the psychological issues surrounding the nomenclature for patients with DSD, previously known by the controversial (and potentially stigmatising) term 'intersex'.

Establishment of a Scottish registry for DSD

Approximately 100 children with DSD are born every year in Scotland; however, the epidemiology of DSD was poorly understood until relatively recently. University of Glasgow researchers sought to address this question by retrospectively analysing data from over 600,000 births that occurred across Scotland during 1988-1997 and uncovered striking regional and temporal variations in the birth prevalence of DSD (2004).[2] These findings indicated that establishing a national registry of affected individuals would be useful for further research into DSD. Consequently, NHS Quality Improvement Scotland (now Health Improvement Scotland) funded Ahmed's team to create the Scottish Audit of Genital Anomalies (SAGA) registry (2003). SAGA established a process for collecting clinical data on all new Scottish DSD cases that occurred between 2003 and 2006 and conducted an audit of variations in clinical management practice across NHS Scotland.

European and international DSD registries

Ahmed went on to develop a bespoke DSD computational virtual research environment (VRE) for paediatric endocrinology in collaboration with Prof. Richard Sinnott (University of Glasgow National e-Science Centre). A VRE is a web-based platform that enables multicentre research collaborations, including data sharing among authorised users. The Glasgow VRE was piloted by a European consortium (EuroDSD) in 2010 as part of a programme to establish a Europe-wide registry of DSD cases (2010).[3] Use of this VRE enabled secure management and dissemination of information held in the registry. In 2011, Ahmed took EuroDSD a stage further by establishing the International DSD (I-DSD) registry, a project co-ordinated by the University of Glasgow that gathers scientific and clinical information on DSD cases from across the world into a single database. University of Glasgow researcher Dr Martina Rodie deputises for Ahmed in the I-DSD

project management group.

The DSD registries expedite clinical research

The DSD registries established by the University of Glasgow have enabled long-term review of how individual DSD cases are managed, and supported additional DSD research projects. For example, Ahmed's team used SAGA to assess the psychological effects of a diagnosis of DSD on the parents of affected children (2007).[4] Their findings revealed the extent to which anxiety over social stigma and treatment outcomes was intensified by inadequate professional support and information. This study was the first to highlight deficiencies in the assistance made available to parents and led Ahmed to call for multidisciplinary input to both the clinical management of patients and the needs of their families. In addition, SAGA data were used to investigate the clinical benefit of diagnostic blood and DNA tests and to explore the genetic basis of specific hormonal causes of DSD (2011).[5] In 2013, Ahmed's group mined the I-DSD database to show that people with rare forms of DSD have a wide range of associated malformations; understanding these conditions may increase the likelihood of reaching a diagnosis and enhance patient care.[6]

Key University of Glasgow researchers: S Faisal Ahmed (Honorary Senior Clinical Lecturer, 2000–2012; Samson Gemmell Chair of Child Health, 2012–present); Richard Sinnott (National e-Science Centre Technical Director, 2002–present); Martina Rodie (Clinical Lecturer, 2010–present).

3. References to the research

1. Hughes IA *et al.* on behalf of the LWPES/ESPE Consensus Groups. Consensus statement on management of intersex conditions. *Arch. Dis. Child.* **91,** 554-563 (2006) doi:10.1136/adc.2006.098319.
2. Ahmed SF *et al.* Prevalence of hypospadias and other genital anomalies among singleton births, 1988–1997, in Scotland. *Arch. Dis. Child. Fetal Neonatal Ed*. **89,** F149-F151 (2004) doi:10.1136/adc.2002.024034.
3. Ahmed SF *et al*. The European Disorder of Sex Development registry: a virtual research environment. *Sex. Dev.* **4**, 192-198 (2010) doi:10.1159/000313434.
4. Duguid A *et al.*, on behalf of the Scottish Genital Anomaly Network. The psychological impact of genital anomalies on the parents of affected children. *Acta Paediatr*. **96**, 348-352 (2007) doi:10.1111/j.1651-2227.2006.00112.x.
5. Rodie M *et al*. Factors that influence the decision to perform a karyotype in suspected disorders of sex development: lessons from the Scottish Genital Anomaly Network register. *Sex. Dev*. **5,** 103-108 (2011) doi:10.1159/000326815.
6. Cox K *et al.* Novel associations in disorders of sex development: findings from the I-DSD Registry. *J Clin Endocrinol Metab* (in press; PDF available on request).

Grant funding

EU Seventh Framework Programme. EuroDSD (e-Health grant 20144). Awarded to RO Sinnott (Principal Investigator) and SF Ahmed (Co-Principal Investigator), 2008-2011, €385,000.
Medical Research Council. The International DSD network (G1100236). Awarded to SF Ahmed (Principal Investigator), M Rodie and RO Sinnott, 2011-2016, £660,157.

4. Details of the impact

A diagnosis of DSD can be devastating for patients and their families; consequently, the clinical symptoms and psychological consequences of DSD must be managed by healthcare professionals with sensitivity and compassion. This aim is best achieved by a multidisciplinary team of healthcare professionals who take a holistic approach to DSD. Clinical management plans should focus on the needs of the patient to ensure that care is individually tailored and targeted to provision of the correct services. In addition, parents and other family members must be fully involved in the decision-making process to help support patients.

Ambitious work conducted by the University of Glasgow has successfully bridged gaps in DSD healthcare provision by establishing: i) the first set of UK clinical guidelines for the initial evaluation and diagnosis of children with suspected DSD; ii) the first managed clinical network and telemedicine service for DSD within NHS Scotland; iii) the first national and international patient

registries for DSD, giving clinicians worldwide unparalleled online access to medical histories of patients with DSD; iv) access to clinical expertise for DSD support groups; and v) an internationally accessible diagnostic advisory service.

UK guidelines

Given the rarity of DSD, very few experts in this condition exist worldwide and clinical care can vary enormously between regions. The development of guidelines outlining best practice is, therefore, paramount to ensuring equality of care. The Society for Endocrinology recognised Ahmed's extensive research and clinical experience in DSD and invited him to chair a UK taskforce to define the most appropriate methods for initial evaluation and diagnosis of suspected DSD. This taskforce developed the first UK set of DSD clinical guidelines, which were published in 2011 in association with nine other UK organisations.[a] Key recommendations included:

- a structured framework of evaluation and diagnosis by a multidisciplinary clinical team experienced in all aspects of paediatric care, including endocrinology, urology, radiology and clinical psychology
- access to a regional DSD centre that specialises in this condition
- essential psychological support for all patients and their families, and access to patient support groups
- contribution of patient data to national and international patient registries

Publication of these guidelines was reported by several health-related media outlets, including *Medical News Today* and *ScienceDaily*.[b]

Managed clinical network and patient registries for DSD

The SAGA study led by University of Glasgow researchers directly shaped the establishment, in 2006, of one of the first managed clinical networks in the UK, the Scottish DSD network (SDSD; previously Scottish Genital Anomaly Network). A managed clinical network is a virtual clinic created to increase standards of care through collaboration and integration of key services. The SDSD network is centralised at the Royal Hospital for Sick Children in Glasgow, with Ahmed as part of the Executive Group that oversees this enterprise. The SDSD network operates a telemedicine clinic service between its major centres in Glasgow, Edinburgh and Aberdeen, accessible by nonspecialist clinicians for advice, case review and as a referral route to specialist centres. The SDSD network also includes a registry that holds data on over 600 Scottish DSD patients, including their diagnosis, recommended investigations, treatments and outcomes. The clinical network team use the SDSD registry as an invaluable resource to inform appropriate diagnosis and treatment of new cases and thereby equalise patient care across Scotland. The SDSD registry has been adopted by the National Services Division of NHS Scotland within its national Clinical Audit Systems, which manages the flow of information through clinical care networks operating within Scotland. Furthermore, the SDSD network has produced a range of patient information leaflets and a management pathway for the care of patients with suspected DSD, all of which are freely available to download from the website. The SDSD has also used the registry to connect families affected by similar DSD conditions.

Internationally, incorporation of data into the I-DSD registry from 23 centres located in 15 countries worldwide (Europe, Middle East and Africa) has created a common dataset with clinical information on the most extreme forms of DSD from 1,161 patients.[c] The I-DSD registry has improved the available knowledge that can be shared on these rare forms of DSD and provided a platform to enhance clinical understanding of their underlying causes. Since 2012, 174 unique visitors have accessed the I-DSD registry website, with 325 visits in total (202 return visitors) and 727 page views; 75 registered users (74 of them return visitors) have logged on to the secure pages of the registry.[d] The I-DSD project page has received 1,162 page views (906 unique).[d] In 2013, a survey of the 134 registered I-DSD users was conducted to assess functionality of the resource.[e] Approximately 30% of respondents were clinicians; around one-quarter of respondents were involved in clinical care, while others were specialists in biochemical or genetic evaluations (27%). More than 30% of respondents logged on to the I-DSD registry every 3 months, with 20% logging on monthly. Some users also provided feedback on their experiences of using the registry.[e] Benefits highlighted included the ability to communicate with other experts and discuss DSD cases; the capacity to transfer patients to another registered user within the I-DSD network should

they relocate to a different country; and the comprehensive clinical data provided.

Clinical expertise for DSD patient support groups

Given the rarity, social stigma and delay in diagnosis of DSD, the role of support groups for patients and parents cannot be overestimated. University of Glasgow researchers have enabled the work of DSD support groups by providing expert advice about these conditions and encouraging participation of the affected community in discussions about education and clinical care.

For example, in 2011, Ahmed provided both clinical content and input to the development of dsdfamilies, an international online resource that provides users with connections to DSD healthcare specialists and testimonials of patient and parent experiences from around the world.[f] The website has around 700-800 individual visitors per month of which 25% are from the UK and 39% from the USA; return visitors account for 20% of all visits. Users from Canada, India, Australia, the Netherlands, Japan, Germany and Spain have also visited the website. In June 2013, the I-DSD convened a conference in Glasgow that welcomed the involvement of patients and support groups.[g] The Administrator of dsdfamilies, who is also a member of the I-DSD Steering Committee, was the opening speaker at this conference and both organised and chaired a parallel session for support groups ("*Meet the Experts – A Joint Effort*"). Ahmed and dsdfamilies secured funding that enabled 16 members of the affected community (parents, adult patients and representatives of other support groups) to attend the I-DSD conference. As a consequence of this session, the Glasgow Working Group was initiated to foster relationships between the affected community (23 members) and clinical staff (27 members) and to progress nine key goals across three functional groups.[f] The Administrator of dsdfamilies stated that Ahmed's influence has two key elements: *"[first] by supporting dsdfamilies he gives legitimacy to the resource which is invaluable when it comes to reaching stakeholders (in both affected and medical communities) and [second] by supporting myself personally and creating the opportunity for me to speak at medical events he gives a voice to the affected community."*

Ahmed has also worked with other DSD support groups. As chair of the Society for Endocrinology taskforce, he invited AIS Support Group and Living with CAH to participate in developing the 2011 UK clinical guidelines.[a] The Society for Endocrinology's dedicated patient support website 'You & Your Hormones' successfully promoted these guidelines,[h] increasing the extent to which reliable information on DSD was publicly accessible and facilitating discussion of concerns, questions and personal experiences of patients and their families online.

Internationally accessible advisory service for DSD diagnosis

Establishing the underlying cause of DSD is vital for directing the appropriate course of long-term clinical care; however, no single facility in the UK offered the combined services of specialist genetic tests for DSD and their interpretation by both scientific and clinical DSD experts. To address this deficit, in 2012, Ahmed established a team of paediatric endocrinologists, clinical and molecular geneticists and clinical biochemists at the Royal Hospital for Sick Children in Glasgow who provide diagnostic advice to nonspecialist clinicians worldwide on a case-by-case basis. There have been 30 separate cases discussed at the DSD diagnostic meeting, 27 of which were from the UK, two from Nigeria and one from Israel (January–July 2013).[i]

5. Sources to corroborate the impact

a. Society for Endocrinology UK clinical guidelines (see Executive Summary, p2) and accompanying press release, 2011
b. Media coverage of UK clinical guidelines, 2011: *Medical News Today*; *Science Daily*
c. I-DSD registry metrics (available on request)
d. I-DSD registry and project page web statistics (available on request)
e. I-DSD registry user survey and feedback (available on request)
f. Statement from the Administrator, dsdfamilies (available on request)
g. I-DSD symposium final programme, June 2013 (p4, 5, 10 and 12)
h. You & Your Hormones patient factsheet
i. Diagnostic advisory service metrics (available on request)