4th I-DSD Symposium

Glasgow, UK

2013

Proceedings of the 4th International Symposium on Disorders of Sex Development

University of Glasgow
7th-9th June 2013

Contents

Welcome Remarks

Dear Friends and Colleagues,

On behalf of the I-DSD steering committee, it is with great pleasure that I welcome you to Glasgow for the 4th International Symposium on Disorders of Sex Development from the 7th to 9th June 2013.

Following the first two meetings in Lübeck in 2004 and 2006, a third meeting was held in 2011 under the EuroDSD banner. All these three meetings had been very successful in attracting a multidisciplinary group of experts who discussed a range of DSD-related issues and laid the foundation for international collaboration. In 2011, the UK Medical Research Council funded a partnership project (I-DSD) which was aimed at sustaining and extending the partnerships developed through the EuroDSD project. The cornerstone to this collaboration is the I-DSD Registry which has registered users from all corners of the world and is fast developing into a professional and scientific network. The programme which has been developed focuses on a range of research which is being performed in a group of rare conditions such as DSD. The meeting will consist of invited speakers and original communications and there will be prizes for the original communications. . In addition to the scientific programme, there will be a workshop for investigators who are interested in performing clinical research in DSD and for those who would like to use the I-DSD Registry.

Glasgow, a city renowned for being the powerhouse of the British industrial revolution has emerged into the 21st century as a city with rich culture and a cosmopolitan outlook. It is one of the top UK destinations for tourism and offers visitors access to the best mixture of museums and galleries, shopping and outdoor adventures. Glasgow is a highly popular conference venue and, this year, the I-DSD meeting will coincide with the annual meeing of RCPCH and Europaediatrics.

The meeting venue is a landmark building that links, within a short walking-distance, the vibrant West End of Glasgow to the original university buildings on Gilmorehill, the venue for the meeting's evening dinner and traditional ceilidh.

Whilst in Glasgow, if you cannot see the distant hills, it is usually because it is raining. When you can see the hills, it means that it is about to rain! We are hoping that some of you will join us for a potentially wet walk in the Loch Lomond area on Sunday afternoon.

We would like to acknowledge the generous support of the Medical Research Council UK

So, once again

Fàilte gu Alba!

Faisal Ahmed and Jillian Bryce

General Information

Meeting Venue:	University of Glasgow Sir Charles Wilson Building, corner of Gibson Street and Kelvin Way
Workshop Venue:	University of Glasgow Wolfson Medical School, Clinical Skills Suite, University Avenue
Internet:	Eduroam (Requires set up via home institute prior to travel) GU Visitor (password issued to registered participants in advance)
Badges:	Name badge upon registration. Permits access to Symposium Sessions and catering facilities. (Does not permit access to DSD workshop - separate registration required)
Meals:	Lunches and coffee breaks included in registration fee
Conference Dinner:	Included in registration fee but limited numbers therefore entry by ticket only (supplied in registration pack).
Accreditation:	Federation of the Royal Colleges of Physicians of the United Kingdom for 18 category 1 (external) CPD credit(s). Certificates of Attendance will be provided at the Symposium.
Organising Committee:	Faisal Ahmed, Jillian Bryce, Karyn Cooper, Martin McMillan, Martina Rodie Ellie Magritte (Family/Support Session), Feyza Darendeliler (DSD Workshop)
Additional Support:	Special thanks to the volunteers from Child Health and NeSC for the additional ground support
Sponsors:	MRC University of Glasgow Scottish DSD Network Yorkhill Children's Charity

Scientific Programme

Friday 7th June 2013

Time			Location
09:00		**DSD Training Workshop for New Investigators** Facilitator: Feyza Darendeliler (Istanbul)	*Wolfson Medical School* *Level 4 Clinical Skills Suite*
12.30	**Lunch (at DSD Workshop)**		*Wolfson Medical School Foyer*
11:30	**Symposium Registration Opens**		*Sir Charles Wilson Building Foyer*
12.00	**Lunch (at Symposium Registration)**		*Sir Charles Wilson Building Foyer*
13.30	**Opening Welcome** Faisal Ahmed (Glasgow)		*Sir Charles Wilson Lecture Theatre (LT)*
13:35	**Session 1. Priorities for the Future** ***(Invited Plenary)***	Chair: Chris Driver (Aberdeen)	*Sir Charles Wilson LT*
13.35	***I-01***	Walking the walk Ellie Magritte (dsdfamilies.org)	
13.50	***I-02***	The approach to the affected child and family Berenice Mendonca (Sao Paulo)	
14.05	***I-03***	DSDnet: Formation of an open world-wide network on DSD Olaf Hiort (Luebeck)	
14.20		Discussion	
15:00	**Coffee break**		*Sir Charles Wilson Building Foyer*
15:30	**Session 2. Oral Communications**	Chair: Laura Audi (Barcelona)	*Sir Charles Wilson LT*
15:30	***O-01***	Young women with DSD their reported experiences of clinical conversations with healthcare professionals. Caroline Sanders (Liverpool)	
15:45	***O-02***	Clinical and genetic characterization of 232 egyptian DSD patients Inas Mazen (Cairo)	
16:00	***O-03***	Gender outcome and sexual functioning in Indonesian patients with a disorder of sex development (DSD) Annastasia Ediati (Indonesia)	
16:15	***O-04***	Phalloplasty for men with DSD and micropenis Nina Callens (Ghent)	
16:30	***O-05***	Management of children with CAH. Time of correction and operation methods of virilized genitales and longterm outcome. Gabriele Jergl-Corkin (Ulm)	

Friday 7th June 2013

Time			Location
17:30	**Evening Lecture**		*Humanities Lecture Theatre*
		Chair:	Ian Ford (Glasgow)
	Quantification in the quest for normality in paediatrics Prof. Lawrence Weaver (Glasgow)		
18:15	End of Day 1	**Free Evening**	

Saturday 8th June 2013

Time			Location
09:00	**Session 3 Drug-Based Therapeutic Interventions**		*Sir Charles Wilson LT*
	(Invited Plenary)	Chair:	Martine Cools (Ghent)
09.00	***I-04***	Hydrocortisone replacement in adrenal insufficiency Richard Ross (Sheffield)	
09.20	***I-05***	Medical therapy for undescended testes Pat Malone (Southampton)	
09.40	***I-06***	The growth of the hypospadiac genital tubercle Pierre Mouriquand (Lyon)	
10.00	***I-07***	Sex steroid therapy in AIS Olaf Hiort (Luebeck)	
10.20		Discussion	
10.45	**Coffee break**		*Sir Charles Wilson Building Foyer*
11:15	**Session 4 Oral Communications**		*Sir Charles Wilson LT*
		Chair:	Antonio Balsamo (Bologna)
11:15	***O-06***	A Multicenter, Interdisciplinary Disorder of Sex Development Registry Patricia Y. Fechner (Seattle)	
11:30	***O-07***	Range and Patterns of Associated Conditions in Disorders of Sex Development: Findings from the I-DSD Registry Kathryn Cox (Glasgow)	
11:45	***O-08***	Cardiovascular pathology in males and females with 45,X/46,XY mosaicism Katya De Groote (Ghent)	
12:00	***O-09***	Copy number determination of sex determining genes by MLPA analysis in patients with 46,XY DSD Annalisa Nicoletti (Bologna)	
12:15	***O-10***	Temporal Changes In Sex Assignment Based On Data Gathered From The I-DSD Registry Zofia Kolesinska (Poznan)	
12:30	***O-11***	Mining a large DSD database: success and failures Rieko Tadokoro Cuccaro (Cambridge)	
12.45	***O-12***	dsd-Life: Clinical European study on the long-term effects of hormonal and surgical therapy and psychological intervention in disorders of sex development (DSD) Birgit Köhler (Berlin)	

Saturday 8th June 2013

Time			Location
13:00	**Poster Session & Lunch**		***Sir Charles Wilson Building Seminar Rooms & Foyer***
14:00	**Session 5 Care and Communication**		***Sir Charles Wilson LT***
	(Invited Plenary)	Chair:	Anna Nordenstrom (Stockholm)
14.00	***I-08***	Supporting the parents of the newborn child Vickie Pasterski (Cambridge)	
14.20	***I-09***	What Do We Know About Behavior in Older Children and Adolescents with DSD Amy Wisniewski (Oklahoma)	
14.40	***I-10***	Applicability of care standards in resource poor countries Jamal Raza (Karachi)	
15.00	***I-11***	Strengths and weaknesses of current research and future directions David Sandberg (Ann Arbor)	
15.20		Discussion	
15.40	**Coffee break**		***Sir Charles Wilson Building Foyer***
16:00	**Session 6 Navigating the Information Highway**		***Sir Charles Wilson LT***
	(Invited Plenary)	Chair:	Liz Crowne (Bristol)
16.00	***I-12***	Making sense of the genetic information Ken McElreavy (Paris)	
16.20	***I-13***	Grappling with steroid metabolomics Nils Krone (Birmingham)	
16.40	***I-14***	The future of rare disease registries Domenica Taruscio (Rome)	
17.00		Discussion	
19:30	**Symposium Dinner & Ceilidh**		***Ferguson Room, One A The Square***

Sunday 9th June 2013

Time			Location
08:50	**Session 7 Management of the Retained Gonad**		***Sir Charles Wilson LT***
	(Invited Plenary)	Chair:	Ieuan Hughes (Cambridge)
08:50		A legal vs medical conflict in management Ieuan Hughes (Cambridge)	
09.00	***I-15***	The genetics of gonadal development Andrew Sinclair (Melbourne)	
09.20	***I-16***	The fate of the gonad in DSD Leendert Looijenga (Rotterdam)	
09.40	***I-17***	Imaging the gonad Margaret Hall-Craggs (London)	
10.00	***I-18***	The practical management of an adult at risk of gonadal tumourigenesis Gerry Conway (London)	
10.20		Discussion	

Sunday 9th June 2013

Time			Location
10.40	**Coffee break**		***Sir Charles Wilson Building Foyer***
11:00	**Session 8 Oral Communications**		***Sir Charles Wilson Lecture Theatre***
			Chair: Ruth McGowan (Aberdeen)
11:00	***O-13***	Modeling Testicular Dysgenesis and Endocrine Disruption in the Human Fetal Testis Rod Mitchell (Edinburgh)	
11:15	***O-14***	Refining the sex determining region located upstream from SOX9 gene. Capucine Hyon (Paris)	
11:30	***O-15***	Preservation of Dysgenetic Gonads - Clinical Outcome Jolanta Slowikowska-Hilczer (Warsaw)	
11:45	***O-16***	Chromatin profiling of germ cell cancer cell lines reveals differences in active enhancer states between Seminomas and Non-seminomas: a GENVIRONMENTAL connection? Yvonne van der Zwan (Rotterdam)	
12:00	***O-17***	Exome sequencing reveals mutations in FOG-2 associated with 46,XY DSD Anu Bashamboo (Paris)	
12:15	***O-18***	Sexual dimorphism of in vivo rodent brain chemistry using Magnetic Resonance Spectroscopy. Martina Rodie (Glasgow)	
12:30	Adjudication of Oral Communications (Panel)		
12.30	**Lunch**		***Sir Charles Wilson Building Foyer***
13.30	**Loch Lomond Trip**		***Coach Collection Point: University Memorial Gate***
17:00	Coach return from Loch Lomond		

Poster Presentations

Sir Charles Wilson Building Seminar Rooms

P-01 Angela Lucas-Herald
The outcome of prenatal identification of a sex chromosome abnormality

P-02 Angela Lucas-Herald
Range of urinary steroid metabolite ratios in children undergoing investigation for suspected disorder of steroid synthesis

P-03 Erin Bergner
News coverage of disorders of sex development, 1993-2012

P-04 Karen Meadley
Neovagina in patients with Mayer–Rokitansky–Küster–Hauser syndrome.

P-05 Wiebke Birnbaum
The decision making process in a case of late diagnosed 5a-reductase deficiency

P-06 Sally Tantawy
Analysis of the gene coding for Steroidogenic Factor 1 (SF-1, NR5A1) in a cohort of fifty Egyptian patients with 46,XY disorders of sex development

P-07 Yvonne van der Zwan
Steroidogenic factor-1 mutations: relation with obesity in humans

P-08 Asmahane Ladjouze
Clinical heterogeneity in patients with NR5A1/ SF1 mutations: About four cases of Algerian patients presenting with 46, XY Disorder of sexual differentiation.

P-09 Nadine Christina Diana Hornig
Transcription analysis of APOD and PPAP2B in genital skin fibroblasts derived from male controls and AIS patients

P-10 Marek Niedziela
A novel Q117X SRY gene mutation in a 46,XY girl with Swyer syndrome

P-11 Scott Shepherd
One for Dex and Dex for all: challenges in the management of congenital adrenal hyperplasia (CAH) in a multiple pregnancy

P-12 Stefan Riedl
Discrepant biochemical findings in a SRD5A2-mutation-negative patient with 46,XY-DSD showing a 5-a-reductase deficiency-typical urinary steroid profile

P-13 Miriam Muscarella
Words that Matter: Improving Medical Conversations and Resources Around DSD for Patients and Families Through Individual Experiences

P-14 Soara Menabò
46,XX DSD with Prader V virilisation, hormonal “conventional” pattern typical for 21-Hydroxylase deficiency (21OHD), and lack of CYP21A2 mutations.

Support Group Parallel Session

Saturday 8th June 2013

Time		Location
09:00	**Support Group Parallel Session**	***Sir Charles Wilson Building Seminar Rooms*** Chair: Ellie Magritte (dsdfamilies.org)
12:30	Session Ends	

Meet the Experts – A Joint Effort

Expertise in dealing with DSD is usually understood as endocrinologists, urologists, psychologists, etc. working together as a Multidisciplinary Team.

But aren't we missing out on the most important discipline? The experts in the everyday life of DSD are those affected by DSD and their families.

So what we need when thinking and talking about optimal care, in all its dimensions, is a joint effort of both kinds of expertise.

This informal meeting brings together our affected community with a more or less equal number of members from the medical community.

This session is primarily by invitation but if you wish to participate please contact the Session Chair, Ellie Magritte (info@dsdfamilies.org)

Please note that access to the Posters/Displays in this seminar room is suspended for the duration of this session. Access will be permitted from 12.30pm

Abstract - Guest Lecture

Quantification in the quest for normality in paediatrics

Lawrence Weaver, Emeritus Professor of Child Health

Science is based on observation and experimentation, and fundamental to both are weighing and measuring. This talk will explore the origins of quantification in the 'scientisation' and 'medicalisation' of child care and the creation of the specialty of paediatrics.

The nineteenth century saw the incorporation of technology, such as the stethoscope, microscope, and thermometer, into clinical medicine. An instrument that has received less attention in the history of medicine is the weighing balance. Although not new to nineteenth century medicine, it played an important part in the rise of the 'numerical method' and the application of 'quantification' to the development and shaping of paediatrics. During its clinical and scientific adoption, the simple procedure of weighing babies was refined and applied in a number of increasingly sophisticated and far-reaching ways: as a measure of the dimensions of the fetus and newborn, as an index of the viability of the newborn, as a means of estimating milk intake, as a way of distinguishing normality from abnormality, as a summary measure of infant health, and as an instrument of mass surveillance. In so doing it changed the way in which medical care was delivered to infants.

Abstracts - Invited Speakers

I-01 Walking the walk

Ellie Magritte (dsdfamilies.org)

We know that developing optimal care for families, children, young people and adults with a DSD demands the input from those who live with these conditions.
We know it requires a much better understanding of the social context in which we live with these conditions.
We know that psychological care is a crucial part of DSD care.
We know there is an urgent want of accessible, educational and practical materials.
We know that long term outcomes for adults appear to be associated with good social support.
We talk about what we know…but putting what we know into practice is all too often lacking…
Thanks to a grant of the Yorkhill Hospital Foundation, some 15 adults and parents, representing various conditions, will attend the I-DSD conference – creating a long overdue opportunity to explore and address users' needs in a constructive and collaborative environment. To maximise interaction over the course of the conference I will start my presentation by introducing all those representing the affected community.
Then, I want to focus on our responsibilities: the responsibility of doctors and parents to care for our young children, and to equip them with knowledge and support, resilience and love so that they can take over the responsibility for their own health and wellbeing as they grow into the contented and self-confident young adults we all want them to be.
What are the challenges to managing our responsibilities effectively and confidently? And what tools can we put in place to do a better job? How can we put all that knowledge we have developed, all that experience we have accumulated, to the best use possible?
We know how to talk the talk, now let's walk the walk.

I-02 The approach to the affected child and family

Berenice B Mendonca, MD, Professor of Medicine
Head of the Division of Endocrinology, University of São Paulo, School of Medicine, São Paulo, Brazil

The birth of a newborn with ambiguous genitalia brings the family and physician's great concern, and this situation must be considered a medical emergency. The first step is to interview the parents. It is important to ask them what they know about the child's problem, which sex do they desire and feel the newborn is. The physician's role is to show serenity and assurance; explain to the parents the principles of sex development; compare genital ambiguity to other congenital malformations; explain that the karyotype does not define gender identity; advice parents on how to explain the disease to their family and friends. A detailed clinical history is very important to determine if there is consanguinity and presence of similar cases in the family, the ethnicity, the use of hormones during pregnancy and the birth weight. On physical examination dysmorphic appearance, size of the phallus, position of the urethra, number of perineal orifices, scrotum hyperpigmentation and the presence of gonads should be evaluated. Laboratory evaluation consists of imaging evaluation and cytogenetic analysis by karyotype or through the presence of the SRY gene by PCR or FISH. Baseline serum levels of sodium, potassium, cholesterol and of the hormones LH, FSH, AMH, ACTH, 17OHP, PROG, 17OHPREG, DHEAS, androstenedione, cortisol, 11-deoxycortisol, aldosterone, Renin, T, DHT should also be performed. Stimulation tests with hCG

and/or ACTH and determination of urinary steroids followed by molecular analysis of candidate genes are other tools necessary to clarify the diagnosis in most of these patients.
My advice to clinicians regarding the approach of DSD patients based in my own experience of more than 450 patients. Keep it simple and work with resources for the laboratory diagnosis and with a trained multidisciplinary team. Only skilled surgeons with specific training in the surgery of DSD should perform these procedures.

I-03 DSDnet: Formation of an open world-wide network on DSD
Olaf Hiort, University of Lübeck, Germany

DSD comprise a heterogeneous group of differences of sex development with at least 40 different entities of which most are genetically determined. An exact diagnosis is lacking in 10 to 80% of the cases, which constitutes an obstacle for the complex management and the prognosis. The European Union has therefore agreed to fund a specific Action in its "Cooperation of Science and Technology (COST) programme, to address the following points: To allow the standardisation of diagnostic and management aspects through the formation of a European Reference Network on DSD; To identify the genetic pathways leading to DSD and create appropriate model systems; To inform and communicate about DSD and foster accessibility and improvement of care. This COST Action will start in late 2013 and is open to all European countries and also to non-European countries.

I-04 Hydrocortisone replacement in adrenal insufficiency
Richard Ross, University of Sheffield, UK

Cortisol secretion follows a distinct circadian rhythm, with circulating levels low at sleep onset, beginning to rise between 02.00 hrs and 04.00 hrs, peaking within an hour of waking and then declining through the day. This circadian rhythm is determined by the central endogenous clock (pacemaker) of the hypothalamic-pituitary-adrenal (HPA) axis, located in the hypothalamic supra-chiasmatic nucleus. The HPA axis plays an important role in maintaining alertness and modulating sleep. Conditions associated with insomnia including depression, sleep apnoea and chronic fatigue disrupt the circadian rhythm of cortisol leading to metabolic abnormalities and increased cardiovascular risk. Patients with adrenal insufficiency have lost the normal circadian rhythm of cortisol and increased morbidity due to fatigue and excess mortality mainly from cardiovascular events and infections. Patients with congenital adrenal hyperplasia (CAH), have an even greater problem because of the challenge of both replacing glucocorticoid and controlling androgen excess. A recent large cohort study in the UK, CaHASE, has revealed evidence of greatly impaired health status in adult patients with CAH. Thus, there is a need for physiological circadian cortisol replacement to address some of these issues. Chronocort is a new approach to delivering hydrocortisone therapy. This modified release formulation replaces the overnight circadian rhythm of cortisol. Pilot formulations have demonstrated the ability to mimic the circadian cortisol rhythm in normal volunteers and studies in patients with CAH have confirmed the ability to control morning androgen levels. In conclusion, there is a need to develop new formulations of glucocorticoid replacement and chronocort provides one option for addressing this challenge.

I-05 Medical Therapy for Undescended Testes

Pat S Malone, University Hospitals Southampton, UK

The undescended testis (UDT) is one of the commonest abnormalities of genital development, affecting approximately 1.5% of boys at one year of age. Testes that remain undescended suffer progressive tubular and germ cell damage that ultimately affects spermatogenesis and future fertility. Consequently current practice recommends that testes should be brought to the scrotum by one year of age, with some recommending surgery as early as 3 months.

Medical therapy, in the form of HCG, was first used in the management of UDT in an attempt to produce testicular descent or to distinguish between retractile and truly undescended testes. It did not work and there was concern that HCG induced apoptotic changes in the germ cells and inflammatory changes in the testes. The Nordic consensus on the management of UDT (2007) stated that there was no role for the use of endocrine therapy and its use to promote testicular descent has been universally abandoned.

However, adjuvant endocrine therapy may have another role. Multiple studies have clearly demonstrated that there is an arrest of spermatogenesis in UDT with a failure to develop adult dark spermatogonia (a surrogate marker of future fertility) even following orchidopexy. The use of adjuvant GnRH has been examined in many studies and the majority demonstrated an improvement in fertility indices, although the level of evidence is of low quality. This presentation will examine this evidence and propose that there is a role for a prospective randomized controlled trial to answer this question once and for all. If we consider that paternity rates are as low as 65% in men with a history of bilateral UDT, all options must be explored to improve this.

I-06 The growth of the hypospadiac genital tubercle

Pierre Mouriquand, Hospices Civils de Lyon – Université Claude Bernard – Lyon , France

An essential aspect of Paediatric Urology and Paediatric Surgery is that surgeons operate on *growing* tissues. It means the tissues used for any reconstruction particularly genitalia will change in size and nature along childhood. It is therefore important to understand how organs grow and evaluate the outcome of surgical reconstruction during childhood, puberty and when the full sized organ is achieved.

The growth of Genital Tubercle (GT) in « normal » children and in DSD patients is a fascinating example of the complexity of the mechanisms acting on this organ from the prenatal period to adulthood. We know little on the cascade of events interacting with the construction of the GT. The aim of this talk is to bring some facts on the construction of the normal and hypospadiac GT and its growth after reconstruction.

What happens for the growth of the hypospadiac GT ? Hypospadias is a development halt of the tissues forming the ventral aspect of the GT. The result of this is a triangular defect whose summit is the proximal division of the corpus spongiosum, the lateral sides are the atretic pillars of spongiosum and the base is the open glans. The tissues sitting inside this triangle do not grow at the same pace as the rest of the GT. This fact is recent ly known and probably explains that surgical techniques solely using ventral tissues (Thiersch – Duplay, TIP) to repair the missing urethra may not have the same satisfactory outcome as urethroplasties combining dorsal and ventral tissues (Onlay urethroplasties) or urethroplasties eliminating immature tissues (Koff). Preliminary studies on the protein platform of the tissues sitting in the triangular defect seem to confirm the imbalance between constructive and destructive proteins and could explain the less sensitive androgen response of these tissues.

Attempts to improve the surgical outcome of hypospadias surgery have been mainly based on preoperative steroid treatment, essentially androgens. Although effects on androgens on the GT growth is well reported, several teams have noticed an increased number of healing complications after this preoperative androgen stimulation. It is also reported by dermatologists that estrogens improve skin healing performance. A double blind study using Promestrien (topical estrogens) vs. Placebo has started two years ago in France and will evaluate the possible differences of complications between these two groups.

I-07 Sex steroid therapy in androgen insensitivity syndrome

Olaf Hiort, Division of Paediatric Endocrinology and Diabetes, University of Lübeck, Germany

Androgen insensitivity describes the inability of cells to respond adequately to androgens. The clinical aspects are well characterized and described in the androgen insensitivity syndrome (AIS), where underandrogenization and feminisation occurs despite normal to high levels of androgens. All individuals with AIS have a distinct hormonal pattern with testosterone and estradiol usually in the upper male reference interval despite their highly variable phenotype ranging from completely female to male. Sex steroid therapy is used in males to enhance further masculinisation and in females if the gonads have been removed. In females after gonadectomy, usually a mono-therapy with continuous estrogens is used for hormone replacement to maintain secondary sexual characteristics and to promote physical and social well-being. However, this has been challenged by some individuals with the complete form of AIS, who reported that this would not correspond to their typical hormone profiles and that they felt diminished in their health-related quality of life. Some women with complete AIS have started with a high dose testosterone therapy, but this practice remains anecdotal until a recently started double-blind clinical trial employing testosterone versus estradiol therapy in complete AIS has been evaluated (www.cais-studie.de). The management of hormone therapy in partial AIS and female phenotype and other forms of DSD may also change in the near future depending on the outcome of this trial. In males with partial AIS, high-dose androgen therapy has been tried with both dihydrotestosterone and testosterone. The dose regime needs to be individually assessed and the outcome individually monitored. So far, a structured clinical trial has not been performed. Further international studies are needed to assess possible endocrine therapies in individuals with AIS and monitor positive and negative effects.

I-08 Supporting the parents of the newborn child

Vickie Pasterski, PhD, Department of Paediatrics, University of Cambridge

The experience of having a child born with ambiguous genitalia and/or be diagnosed with a disorder of sex development (DSD) is increasingly being understood as a traumatic event for parents. Though not all presenting cases are life-threatening, the event may nevertheless be experienced as a threat to the integrity of the child. Supporting the parent in this scenario is increasingly being incorporated into the clinical care model. In addition, while the distress that parents experience has been well documented, evidence-based protocols for relieving parental distress are only just emerging. Recent data suggest that uncertainty on the part of the parent(s), which can go on for as long as it takes to reach a diagnosis, is predictive of reported levels of stress. Uncertainty in terms of the process of typical sexual differentiation and how it relates to a specific

diagnosis and prognosis may be alleviated with the provision of educational materials and interpersonal support from the multidisciplinary team. However, in some cases, additional intervention may be warranted. An evidence based model for treating and supporting families which identifies events such as diagnosis and emergent medical care as *potentially traumatic events* and articulates that it is the interaction between the objective nature of the event and the subjective interpretation of the event which renders it as traumatic or not may prove useful in cases of DSD, but has yet to be tested. Such a model will be discussed along with the potential ramifications of uncertainty within the DSD-related medical field itself. For example, the evolution of clinical management, including issues pertaining to diagnostic classification, management of undiagnosed cases, and approaches to surgical interventions, will be considered.

I-9 What do we know about behavior in older children and adolescents with DSD?

Amy B. Wisniewski, PhD, Department of Urology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Children with DSD develop aspects of their gender that are discordant with their genetic, hormonal and/or social sex. An explanation of the role of sex chromosomes, androgen exposure and learning on the development of gender and other behaviors in children and adolescents with 46,XX and 46,XY DSD will be given. Additionally, consideration of parents' responses to their child's condition and associated medical and surgical treatment will be offered. From these data we can evaluate what is known about several influences that significantly impact behavioral development in children and adolescents with DSD, as well as suggest new areas of study to improve outcomes for affected children and their family members who care for them.

I-10 The Constraints of DSD Applications in Resource Poor Countries

Syed Jamal Raza, National Institute of Child Health, Karachi, Pakistan

Islamic Republic of Pakistan is situated in South East Asia is the 7th most populated country in the world. With only three paediatric endocrinologist and twenty adult endocrinologist for an approximate population of over 180 million, facilities for DSD are scarce and non-existent. In a few major cities where facilities are present they are extremely expensive and are out of reach for the general population. Various concerns and constraints have been identified during our 15 year experience of treating DSD patients. These range from religious, cultural, social, and financial to limited facilities available for investigations and treatment. DSD patients and their families face unprecedented discrimination from society which begins right after the birth of the child. Being a male dominated society blame often falls solely on the woman. Due to all these issues a unique culture of "Hijra" has automatically developed in society as people learn to cope with the untreated psychological trauma of DSD. These Hijras were often employed as late as the Mughal Emperors as they were able to move freely among segregated sections for females and males. Until last year they for centuries have never been given full civil rights.
We will be discussing these constraints with a case based approach so that this dilemma can be clearly understood as DSD practice in Pakistan consists of making the most of what inadequate facilities we have available. The impact from international partnerships is immense as much needed genetic screening is made available free of charge to our patients.

I-11 Strengths and weaknesses of current research and future directions

David E. Sandberg, University of Michigan Medical School, Ann Arbor, MI, USA

Background

Persons born with disorders of sex development (DSD) have presented researchers with opportunities to examine the influence of biological (ie, genetic and hormonal) factors on the process of psychosexual differentiation (gender identity, gender role and sexual orientation). Research findings, commonly published in medical journals, are potentially misleading and confusing to health care providers, affected persons, and families regarding their import for clinical management (eg, significance of gender-atypical behavior). Further, relatively little consideration has been given to social contextual factors that mediate (eg, physical appearance, body-image, homophobia) or moderate (eg, family ethnic or religious background and associated beliefs) the effect of biologic factors on developmental outcomes. An overemphasis on biological predictors of gender-related outcomes may also have been associated with a scarcity of studies investigating condition-specific factors (eg, stigma and associated secrecy) and clinical management practices (eg, genital surgery, their complications and repeated genital examinations) that conceivably influence gender and other health-related quality of life outcomes. Finally, the majority of studies have been quantitative, employing standardized measures to assess behavior in predetermined domains. Relatively few studies employed qualitative or mixed methods.

Aim

Propose the hypothesis: developmental trajectories in chronic pediatric conditions (ie health-related quality of life), including DSD, are influenced as much by the psychosocial environment, supports, and organization of health care delivery as by the specific nature of the person's medical condition.

Discussion

Adopting a "noncategorical" approach to DSD clinical care and outcomes research that takes mediating and moderating factors into account will accelerate discovery and improvements in care by opening this set of rare conditions to advances in other areas of pediatric and behavioral health care.

I-12 Making sense of the genetic information

Ken McElreavey, Human Developmental Genetics, Institut Pasteur, France

Next generation sequencing technologies are dramatically changing biomedical research and patient diagnosis. The plummeting costs of exome and whole genome sequencing as well as robust experimental and computational protocols means that this technology is becoming available to most laboratories. However, the identification of disease-causing mutations in individuals with DSD and DSD-related phenotypes such as cryptorchidism and hypospadias will be challenging. The following factors needs to be considered for an accurate genotype to phenotype correlation

(i) Defining the phenotype

The availability of the genomic sequence of an individual with DSD highlights the need for a highly accurate clinical description of the phenotype using a standardized precise protocol. For some DSD

phenotypes, such as gonadal dysgenesis or ovotesticular DSD, this is relatively straightforward but it is less so with cases of undervirilised 46,XY DSD and especially those who are raised as boys. These cases are often investigated to a variable extent and for the majority the aetiology remains unclear. The situation with non-syndromic hypospadias is even more complicated. Hypospadias is considered multifactorial with contributing genetic and environmental factors. Familial clustering without a clear inheritance pattern has been reported suggesting a genetic component, however genetic association studies have for the most part failed to identify the pathogenic gene. Rare mutations have been identified in association with hypospadias and are mainly associated with severe posterior forms rather than the distal or glandular forms. This suggests that environmental factors may predominate in the milder glandular forms of hypospadias perhaps in genetically susceptible individuals. If we are to precisely determine the genetic basis of these phenotypes we need to accurately record subtle differences in clinical measurements including those obtained through non-conventional approaches such as metabolomics.

(ii) Genetic heterogeneity

Genetic heterogeneity refers to the degree to which a single phenotype/disease is caused by multiple loci amongst different patients. The degree to which DSD displays extensive genetic heterogeneity is unknown but could be extensive. For example, the androgen receptor has been reported to interact with hundreds of cofactors. There are many online tools available that help to interpret genetic data such as defining gene ontology and pathway analyses and these may help to link the disease variant with the phenotype. However, where a considerable number of novel genes are involved a large numbers of subjects may be required to attain sufficient power to identify variants causing and modulating the expressivity of the phenotype. Increasing the size of the patient cohort will increase the power to discover disease-causing variants. This is particularly important for DSD, where familial cases that could help to link the phenotype with the genotype are rare.

(iii) Functional studies

The definition of the patient phenome together with extensive genetic and other -omic datasets must be supplemented by functional in vitro, ex-vivo and in vivo models to dissect the molecular pathways underlying the pathology and giving not only diagnosis to all patients with DSD but also potential personalised therapies.

If we are truly to make sense of the genetic data, it will require a strong multi-center and multidisciplinary approach. Combining the expertise of international clinical and research centers through initiatives such as I-DSD is essential if we are to understand the genetic basis of DSD.

I-13 Grappling with steroid metabolomics

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Disorders of steroidogenesis have been primarily studied through quantification of selected analytes by immunoassays. Structural similarity of steroids compromise specificity of immunoassays by crossreactivity, and immunoassays are notoriously inexact in low concentration ranges as seen in paediatrics. During recent years laboratory investigations of patients suffering from potential endocrine conditions has become more accurate. High-performance liquid chromatography/ tandem mass spectrometry (LC-MS/MS) is the most successful approach to improve specificity problems inherent in many immunoassays and has become the method of

choice for clinical steroid analysis. LC-MS/MS is increasingly replacing immunobased techniques because of its high sensitivity, greater specificity, high reproducibility and ability to analyse multiple steroids from small sample volumes simultaneously. LC-MS/MS is a highly valuable second-tier test in CAH newborn screening and is enhancing diagnostic capabilities of routine testing particularly when steroid profiles are available. However, LC-MS/MS is of limited use in defining novel metabolomes. Gas chromatography mass spectrometry (GC/MS), in contrast, is unsuitable to rapid high sensitivity analysis of specific compounds, but is the most powerful discovery tool for defining steroidobolomes. GC/MS has defined several metabolomes with the most recent being apparent cortisone reductase deficiency and P450 oxidoreductase deficiency. Almost all steroidogenic conditions are defined by the absolute concentration of steroid metabolites, many are diagnosed between ratios of substrate metabolite to product metabolite of enzymatic reactions. Such methods are sensitive enough to distinguish between the differential impairment of 17, 20 lyase caused by mutations in either CYP17A1, POR or cytochrome B5. A particular benefit of GC/MS is its non-selective nature; a scanned run will contain every steroid excreted, providing an integrated metabolome. The analysis of such “undefined” metabolomes using i.e. biocomputational analysis by supervised machine learning tools provides the opportunity for identification of novel metabolomes and characterisation of novel steroidogenic disorders causing DSD.

I-14 The Future of Rare Disease Registries

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Rare diseases (RD) have become in the last years a hot topic of public health all over the world. In Europe, the EU Council Recommendation on RD (2009) stimulated the development of national plans or strategies in the EU Member States, a wide array of coherent actions to improve care of RD patients, which included international cooperation and the development of registries. More recently, the EU Directive on Cross-Border Health Care (2011) identified RD as the paradigmatic topic to start development of cooperation and of European Reference Networks, through which clinical data are shared. At the same time, an International research consortium (IRDiRC) has been established for research into RD and development of new orphan drugs. This initiative, initiated by United States and EU, has been joined individually by Japan, Canada and several EU Countries; further countries are negotiating to join it. All these initiatives have triggered a number of projects, which, with different but partially overlapping methods and scopes, promote data sharing and interoperability: EPIRARE, PARENT, RD-Connect and EUROCARE. All these activities change the perspective of RD registries and will mark a transition from spontaneous registries, often resulting from specific research interests and with difficult sustainability, to a more coordinated system of registries. This system should assures a number of outputs of use to the different funding stakeholders, and provides tools, resources and a quality assurance environment to the participating registries without hindering the development of research studies. It is expected that such transition will also result in higher confidence of patients and in higher numbers of registered patients. The main features of this system will be discussed.

I-15 The Genetics of Gonad Development

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Disorders of sex development (DSD), ranging in severity from genital abnormalities to complete sex reversal, represent a major clinical concern. The cause of these disorders is most often a disruption of the genetic programs that regulate development of testes or ovaries. Alterations in the key testis genes SRY, SOX9, FGF9 and ovary genes such as RSPO1, WNT4, β-catenin, FOXL2 are associated with DSD. In addition, NR5A1 affects multiple points in the gonad and steroidogenic pathway and defects in it are associated with many forms of DSD. Despite this knowledge in many cases of DSD the causative mutations are not known. We have identified copy number changes identified rearrangements that affected known and novel gonad genes. Known genes affected included: a deletion in the upstream regulatory region of the *SOX9* gene in a 46,XY DSD individual. Amongst other potentially causative findings were rearrangements affecting the X-linked *SOX3* gene in three unrelated 46,XX DSD patients. This is the first evidence in humans that *SOX3* may be functionally interchangeable with the testis gene *SRY*. We were also able to demonstrate that mutations in the MAP3K1 gene cause testis failure. This suggests a new signaling transduction pathway is involved in testis determination. These analyses give new insights into the molecular genetic pathways underlying human gonad development and dysfunction. Our data have generated a number of new candidate genes for future diagnostic screening.

I-16 The Fate of the Gonad in DSD

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Various risk factors have been identified for development of so-called type II malignant gonadal germ cell tumors (GCC), i.e., seminomatous and nonseminomatous cancers. These include cryptorchidism, infertility, a previous GCC, familial predisposition, as well as specific forms of DSD. These latter include patients with gonadal dysgenesis and hypovirilization combined with presence of a specific part of the Y chromosome, known as GBY (GonadoBlastoma on the Y chromosome). TSPY (Testis Specific Protein on the Y chromosome) is one of the likely candidates to be involved. The precursor lesion of GCC can be either Carcinoma *In Situ* (CIS) of the testis, or GonadoBlastoma (GB) of the dysgenetic gonad. The germ cells affected are embryonic in origin and characteristically express markers like OCT3/4, SOX17, c-KIT etc. The supportive cells are Sertoli cells, recognized by SOX9, in CIS and Granulosa cells, recognized by FOXL2, in GB. Dependent on the level of "Testicularization", either CIS or GB, or a mixture of both precursor lesions can be found. SCF, also known as KITLG, is reported to be informative to distinguish the earliest (i.e., pre-) malignant germ cells from embryonic germ cells showing only a delayed pattern of maturation. This is suggested to be related to a temporarily autocrine loop, which is of specific interest because of the recent linkage found to Single Nucleotide Polymorphisms (SNPs), related to genes involved in early gonadal development, including KITLG. Based on the current knowledge of normal gonadal development as well as the pathogenesis of GCC, a clinical decision tree is presented informative to identify and monitor DSD patients for their risk to develop this kind of cancer. Clinical implementation of such a proposal will prevent unnecessary treatment (including gonadectomy) on the one hand, and underdiagnosis on the other.

I-17 Imaging the Gonad

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Imaging of retained gonads is performed for a number of reasons

1. To identify their presence or absence
2. To monitor changes that suggest malignant transformation
3. For image guided biopsy

The most common gonads imaged are retained testes in XY DSDs. The methods of choice for imaging are ultrasound and MRI. Ionising radiation (such as CT) should be avoided for imaging any gonad. Ultrasound is a useful tool for imaging gonads sited in the inguinal canals, but is less good for visualizing pelvic and abdominal gonads where they may be obscured by bowel loops.

Retained testes in the presence of a DSD have abnormal appearances compared with 'normal' testes. In a study we performed reviewing the MR imaging and histology of patients over 16 years with CAIS and retained gonads, we found that the testes were smaller than in the normal male, and over 50% contained low signal nodules. These corresponded histologically with Sertoli adenomas. The majority of testes show small paratesticular cysts. In our series the small number of testes with premalignant change could not be identified on MRI.

There are currently no data to suggest that imaging can be either sensitive of specific for identifying malignant changes. The rate of progression from non-malignant, to pre-malignant to invasive tumour is not known for certain and therefore the length between imaging examinations is currently arbitrary. Newer tools such as cell tracking techniques might hold potential for the future.

I-18 The practical management of an adult at risk of gonadal tumourigenesis

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Care of adults with DSD poses many challenges not least because most information in the field is based entirely based on paediatric experience. There is little guidance for making an accurate diagnosis in adults with a female phenotype who might present with amenorrhoea bypassing paediatric services or who have had a previous diagnostic workup that cannot be verified. Furthermore, the group of women often over that age of 25 for whom paediatric care might not have been transparent in terms of accurate diagnostic information, may have a legacy if psychological issues that hinder engagement with medical services.

In the surgical field, adults with DSD have to cope with variable outcomes from genital surgery that require ongoing care. Medical aspects of an adult DSD service include optimisation and an individual approach to sex steroid replacement as well as long-term health surveillance such as monitoring bone density and cardiovascular risk.

In a world where individuals attending an adult DSD service are often highly informed experts in the field, the role of medical care is often to guide on safety aspects and accept that the evidence base from which conventional practice has developed is questionable. One example of this area is the practice of gonadectomy for women with complete androgen insensitivity syndrome for whom there is very little data in adults but at the same time a practical approach has to be developed to follow individual expectations.

Abstracts - Oral Communications

O-01 Caroline Sanders

Young women with DSD their reported experiences of clinical conversations with healthcare professionals.

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Background: Young women's experiences of learning about their DSD and their interactions with health care professional are under reported. Aim: To explore young women's expectations of and experiences of clinical conversations. Methods: Young women in the UK were interviewed or completed a diary (2011-12) focusing on their experiences of clinical conversations with a range of healthcare professionals. An IPA approach was used to analyse these data. Results: Thirteen young women (43%, n=13/30, 14-19 years, mean 16.8 years) with a range of DSD conditions participated. The theme 'communication with professionals; impact on identity and autonomy' is reported here. The young women experienced tensions in communication arising from the unpredictability of which professional they saw and what information their parents had shared previously. They needed more information about their own clinical history and their DSD trajectory to facilitate decision-making. Gathering information was problematic; they felt that professionals' assumed that parents had the knowledge, capacity, capability and willingness to share complex DSD information. However, parental information was perceived to be subjective and edited. Good communication skills, respect, privacy and opportunity were seen to be essential to successful engagement and participation in clinical conversations. Discussion: Professionals need to provide objective information so that young women can fill in the gaps in their knowledge about themselves thus challenging the insecurity brought about by uncertainty or ignorance. Young women believed knowing, trusting and building confidence over a period of time with health professionals were fundamental to supporting effective clinical conversations. Young women often felt their local health provider should manage their everyday health needs while specialist services would be best suited to helping them understand their DSD. Conclusion: In order to overcome the asymmetry of knowledge within clinical conversations between professionals, parents and young people ways to improve communication share knowledge and support participation are needed.

O-02 Inas Mazen

Clinical and genetic characterization of 232 Egyptian DSD patients

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Background Disorders of sex development (DSD) comprise a heterogeneous group of heritable abnormalities of sexual determination and differentiation. In Egypt the incidence of DSD is 1 in 5 ,000 , due to the high rate of consanguinity Aim of study This study is among a project funded by NRC aimed at proper classification of DSD patients to establish a precise diagnosis to offer a better genetic counseling . Methods Karyotyping , FISH in blood and gonads and sequencing of SRY , AR, HSD17B3, SRD5A2 and SF1genes. Results The study included 232 patients with variable presenting features, referred to the Human genetics clinic during the period 2011-2012. Abnormal karyotypes were detected among 129 patients and represented different arrays of chromosomal anomalies. Numerical sex chromosomal abnormalities included 45,X karyotype, occurring in pure or mosaic

forms (51 patients), 47,XXY (53 patients), 47,XXX (4 patients) and 49,XXXXY (one patient). Structural sex chromosomal abnormalities were seen in 36 patients, either in a pure form or associated with 45,X mosaicism. They included iso (Xq) abnormality (21 patients), isodicentric Y chromosomes (9 patients), ring X (3 patients), X;Y translocation, , add (Xq) and del (Xp) (one patient each). XX testicular DSD was found in 4 patients, one of them presented with Down syndrome. Autosomal abnormalities were detected in 6 patients in association with other congenital anomalies. Molecular analysis was done for 45 patients with 46,XY DSD. Nine patients showed different mutations in HSD17B3 gene, including a novel one. Another novel mutation of AR gene was detected in a large family. SF1 mutation was found in 3 patients and G34 R mutation was found in SRD5A2 gene, confirming the gene founder effect. Conclusion This extensive study added more informative clinical, cytogenetic and molecular data and reflected the heterogeneity of Egyptian DSD patients.

O-03 Annastasia Ediati

Gender outcome and sexual functioning in Indonesian patients with a disorder of sex development (DSD)

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Background: In Indonesia, comprehensive treatment for individuals with DSD became available recently. Consequently, many affected individuals had been living untreated or received treatment late in life and have been raised in an ambiguous body and gender. Objective: To investigate gender identity, gender role behaviour, and sexual functioning in patients with DSD. Patients were compared to healthy controls matched for gender, age, and socio-economic background. Methods: Subjects: Cross sectional study comparing 116 patients aged 6-41 years and 116 healthy matched control subjects. Materials: Gender identity and gender role behaviour was measured using Indonesian versions of GII and GIQC for children; Activities and Gender Questionnaires for adolescents/adults. Sexual functioning was measured only in adults using Indonesian versions of FSFI, FSDS-R and MSHQ. Statistical analysis: Principal Component Analysis and Cronbach's alpha were applied in measuring construct validity and internal consistency. Differences between patients and controls were compared using Mann-Whitney U-test. Results: Social gender role change was reported in 20/116 (17%) patients: 4/60 (7%) children; 2/23 (9%) adolescents and 14/33 (42%) adults. All changed from female to male. Patients living as girls reported more often long-term gender-related problems (i.e. affective gender confusion and cross-gender role behaviour) than their matched controls did. 14/18 (78%) adult women and 7/21 (33%) adult men never had sexual/romantic relationships. Taboo, fear of ostracism, and infertility were the reported as main reasons for delay or refusal in entering a romantic relationship. Women experienced great distress due to infertility. Discussion: Particularly women are disadvantaged since gender identity problems largely occur among patients assigned female at birth, and infertility causes distress in a collective-driven society that expects procreation. Conclusion: Many untreated or late-treated patients experience gender identity problems. Counselling and

education on DSD is prerequisite to promote social acceptance of DSD. Follow-up is needed to compare late-treated with early-treated patients.

O-04 Nina Callens

Phalloplasty for men with DSD and micropenis

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Background: The term 'micropenis' encompasses a range of congenital and acquired conditions resulting in an abnormally short penis. Small penis size may persist into adulthood, becoming a major cause of dissatisfaction. Can phalloplasty, generally applied in the context of transgender surgery, be a valuable treatment for men with micropenis? Objective: We aimed to assess long-term (> 1 year post surgery) sexual Quality of Life (QoL) outcomes after phalloplasty in 46, XY male patients with penile insufficiency. Methods: Ten men (20 - 43 years) received phalloplasty (8 with radial forearm free flap and 2 with anterolateral thigh flap) between March 2004 and June 2011 (follow-up, 14 to 92 months). All but one had erectile implant surgery approximately 1 year after phallic reconstruction. All patients received psychological counseling before and after surgery. Sexual QoL was assessed with a semi-structured interview. Results: All men suffered from their condition before surgery, with low self-esteem and sexual dysfunction. After phalloplasty, all men reported a boost in self-confidence, and experienced orgasm with ejaculation. However, 60% was still afraid of partner reactions and sexual rejection or had trouble with the use of the erection prosthesis, making sexual enjoyment not obvious. Neophallus sensitivity was said to be poor and scars at the donor site were important. Five men developed urinary complications (stricture or fistula) and in one man the erectile implant had to be removed because of an aneurysmal swelling. Nevertheless, all indicated they would choose again for phalloplasty if necessary. Discussion: Phalloplasty opens new horizons for the treatment of 46, XY DSD patients with penile deficiency, but limitations of the technique should be emphasized prior to surgery. Psychological support should be an integral part of the management in alleviating the distress and impairment of sexual QoL. Publication of series with large numbers and longer follow-up is needed.

O-05 Gabriele Jergl-Corkin

Management of children with CAH. Time of correction and operation methods of virilized genitales and longterm outcome.

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We would like to present the management of children with CAH at the University Hospital Ulm, Germany. The timing of the correction of virilised genitalia is still discussed controversially. At our center, children and parents are investigated and counseled in a special outpatient clinic for DSD by pediatric endocrinologists, pediatric psychologists, social workers, geneticists and pediatric surgeons, who are specialized in this field. It is mandatory to discuss all aspects concerning the timing and method of the operation extensively and individually with every family. All patients are regularly followed up. The medical transition to the adult specialists is planned at the end of puberty. Having learned over the years from the psychological and sexual problems CAH patients can encounter we have optimized our technique and adapted it to the individual patient. We will briefly present our operation methods. In treating adult CAH patients, who were previously operated with other techniques/other centers and who were unhappy of the insufficient cosmetic and functional results, we gained further experience and developed own techniques for revisions. Over a 27 year period our specialized pediatric surgeon has operated over 600 children with CAH, performing clitoris reductions, vaginoplasties and reconstructions of the labia. In this follow-up study we present the outcome of 126 patients aged 17-25 years. All of them had surgical corrections as an infant. In conclusion, the best results are obtained when the correction of virilized genitalia is performed in infancy and not in puberty. There are less psychological problems. All patients have to have a good follow up and should be told the whole truth about their malformation. If that is the case puberty is no greater problem as in other girls. The mayor goal in treatment of CAH patients is a happy child with a normal possibility of sexual development.

O-06 Patricia Y. Fechner

A Multicenter, Interdisciplinary Disorder of Sex Development Registry
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Background: The care of individuals with Disorders of Sex Development (DSD) requires evidence-based clinical practice guidelines which have been lacking due to the low incidence of many DSD. Objectives: Using an interdisciplinary team approach, the DSD-Translational Research Network (DSD-TRN) seeks to inform evidence-based care through standardizing diagnostic and treatment protocols. With reduced variation in clinical practice and enhanced patient and family healthcare-related experiences improved quality of life outcomes are expected. Methods: The DSD-TRN consists of four medical centers (Seattle Children's Hospital; University of California, Los Angeles; University of California, San Francisco; University of Michigan) and a non-governmental health care organization with representation from the major DSD advocacy organizations (Accord Alliance). The governance structure includes a leadership group and four workgroups, each with specialty and network site representation: Anatomy/Surgery, Endocrinology, Genetics, and Psychosocial. Workgroups have defined data elements to be included in the comprehensive registry that track the process of diagnosis and ongoing clinical management in all domains. Results: Data collection forms have been prepared and are being integrated into ongoing patient care as each center receives institutional review board approval. The goal is to populate the Registry with 800 participants. Discussion: Although consensus for many assessments and procedures was established (eg, uniform terminology, exams and laboratory studies performed), a decision was made to have the Registry capture variability where consensus remained elusive. Analysis of registry data will focus on the associations between variability in clinical practices and a range of outcomes. Conclusion: Through the process of defining data elements for a registry, we have begun the process of standardizing care for persons with DSD. The ultimate goal of this effort

is expanded discovery for this set of rare disorders and establishment of evidence-based best practices.

O-07 Kathryn Cox

Range and Patterns of Associated Conditions in Disorders of Sex Development: Findings from the I-DSD Registry

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Background: Improved knowledge of the range of anomalies encountered in DSD may improve our understanding of the underlying aetiology. However, given the rarity of these conditions, thorough analysis of congenital anomalies in DSD has not previously been possible. Aims: To discover the frequency of associated conditions in DSD, and to identify patterns of anomalies within specific disorders. Methods: 1050 registered cases on the I-DSD Registry (UKCRN#12729), currently used by 20 clinical centres in 14 countries, were examined. 649(62%) had consent level to allow sharing suitable information. Case details were obtained from the Registry and where information was unclear the reporting clinician was contacted to obtain further information. Results: Of 649 cases, congenital anomalies occurred in 173(27%); 107(62%) cases had one anomaly and 66(38%) had two or more anomalies. Commonest anomalies included renal-35(20%), heart-32(18%), skeletal-32(18%), short stature-30(17%), small for gestational age(SGA)-28(16%) and CNS-27(15%). Of the 46XY, 46XX and 45X/46XY cases, anomalies were encountered in 113(25%), 31(26%), 19(45%), respectively. In complete androgen insensitivity syndrome(AIS), congenital anomalies were reported in 8 cases reported to have a mutation in the androgen receptor(AR) gene (ARmut+ve) (range of anomalies: renal, GI tract, heart, skeletal, skin) and in 1 case which was ARmut-ve (renal). Corresponding data for partial AIS: total 10 cases, 2 ARmut+ve, 3 ARmut-ve, 5 unknown. Of 89 cases of non-specific 46XY DSD, associated anomalies were encountered in 43(48%). The range of anomalies included SGA-17(40%), heart-10(23%), CNS-8(19%), renal-7(16%), GI tract-6(14%), ENT-5(12%), skeletal-5(12%), craniofacial-4(9%), short stature-4(9%), eyes-3(7%), respiratory-3(7%), skin-3(7%), adrenal-1(2%), haematological-1(2%), unidentified syndrome-1(2%). Conclusions: Associated congenital anomalies occur frequently in DSD, including in monogenic conditions such as AIS which are generally thought to solely affect sex development. These findings provide a direction for further study of genetic and environmental causes of DSD.

O-08 Katya De Groote

Cardiovascular pathology in males and females with 45,X/46,XY mosaicism

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Background: The phenotype of 45,X/46,XY mosaicism is heterogeneous ranging from females with Turner syndrome (TS) to apparently normal males. Males with 45,X/46,XY frequently show stigmata typically associated with TS. We hypothesised that males with 45,X/46,XY have similar cardiovascular pathology as females with 45,X/46,XY. Objective: To investigate cardiovascular abnormalities in 45,X/46,XY males and to compare them with 45,X/46,XY females Methods: Patients with 45,X/46,XY mosaicism were selected from the Belgian Registry for Growth and Puberty problems and via the multidisciplinary clinic for disorders of sexual development. They underwent a complete cardiac examination with blood pressure measurement, ECG, echocardiography and MRI. Clinical features and external masculinisation score (EMS) were retrospectively collected from the medical files. Results: Eighteen patients were included: 8 raised as females (F) and 10 as males (M). Seven F had classic TS features with typical female external genitalia and short stature; one child with ambiguous genitalia at birth was raised F. Four M were born with typical male external genitalia (EMS 12/12). Four showed milder (EMS 8-10/12) and 2 severe (EMS 5-6/12) degrees of undervirilisation. In the 45,X/46,XY M, phenotypical features associated with TS were frequent. A structural heart defect was diagnosed before inclusion in 1 F with coarctation and 1 M with spontaneously closed VSD. A bicuspid aortic valve was found in 8 (3F, 5M). Dilation of the ascending aorta was present in 4 M and was severe in 2 young boys. QTc was prolonged in 3 F and 2 M. Conclusion: Males with 45,X/46,XY mosaicism, also those with normal external genitalia or mild undervirilisation, have similar cardiovascular pathology as 45,X/46,XY females. Dilation of the ascending aorta can be important, also in males. We advise cardiac screening and life-long monitoring in all males with 45,X/46,XY mosaicism according to the existing guidelines for Turner syndrome.

O-09 Annalisa Nicoletti

Copy number determination of sex determining genes by MLPA analysis in a patients with 46,XY DSD.

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Background. Gene dosage mechanism is the basis of action of sex determining genes, such as NR0B1, WNT4, SOX9 and NR5A1. In 46,XY DSD patients (in particular with complete/partial gonadal dysgenesis, GD) the analysis of copy number variation (CNV) of these genes is part of the diagnostic tests already with the screening of mutations in SRY gene, the major candidate for 46,XY GD. Objective. We studied CNV of sex determining genes in a patient with 46,XY partial GD that was negative for point mutations in SRY gene. Methods. The CNV was determined by MLPA analysis using MRC Holland Kit P185, containing several probes for SRY, NR0B1, WNT4, SOX9 and NRA51 genes, in genomic DNA from peripheral blood. The data analysis was performed by Coffalyser software. Results and Discussion. We identified a duplication of NR0B1 gene, the candidate for the X-linked 46,XY GD. The first reports come from patients with Xp region

rearrangements and complex phenotype including sex reversal. A minimal common region of 160-kb was determined containing the NR0B1 gene, and regulatory sequences at hundreds kb upstream of NR0B1 gene were also recently identified. Actually it is confirmed its role in sex determination as an anti-testis gene, but animal model show a more complex function of NR0B1 in both sex changing over time and finely regulated. The genotype-phenotype correlation is therefore not well delineated, the severity of phenotype range from reduced testicular size and impaired germinal epithelium development until complete sex reversal. This is the case of our patient, diagnosed at 4 yrs of age as 46,XY GD, presenting genital virilization at 10yrs, with hormonal finding of partial hypergonadotropic hypogonadism, then diagnosis was corrected in partial GD. Conclusion. These data confirm that the analysis of CNV in the NR0B1 gene locus must be recommended in the majority of 46,XY DSD cases.

O-10 Zofia Kolesinska

Temporal Changes In Sex Assignment Based On Data Gathered From The I-DSD Registry

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Introduction: It is unclear whether the proportion of children with DSD who are assigned a male sex or a female sex has changed over time. Aim: The aim of the analysis was to determine whether the appearance of the external genitalia assessed by the initial external masculinisation score (EMS) influenced the choice of sex of rearing and whether this changed over time. Methods: The analysis was performed on the data gathered in I-DSD Registry until February 2013. We defined the initial external masculinisation score as the EMS assessed in the neonatal/infancy period or in older cases as the EMS before any intervention. The cases were divided according to year of birth into three groups: those born before 1990, from 1990 till 1999 and born after 1999. Results: In partial androgen insensitivity syndrome (total n=109) the number of cases of male sex assignment (n=78) as well as the proportion of such cases (from 1,38 to 5,29) increased over time. There was a significant difference in the initial EMS between the group raised as boys (median 6, range 2-11.5) and the group raised as girls (median 2, range 0-8) p=0,000000. This significant difference of the initial EMS between the two sexes was observed over time. However, there was no significant difference in the initial EMS over time in the group raised as girls or in the group raised as boys. In fact, the degree of overlap for the initial EMS between the two sexes increased with time. Discussion: These data clearly show that there are clear trends in sex assignment and that they have been influenced by factors other than the appearance of the external genitalia. There is a

need to explore the underlying reasons for these trends. The project was possible due to the ESPE Visiting Fellowship awarded to ZK in September 2012.

O-11 Rieko Tadokoro Cuccaro

Mining a large DSD database: success and failures

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Background The Cambridge DSD Database contains clinical, biochemical, histological and genetic information on patients with 46,XY DSD, currently totalling 1800 cases. Aim To review the data to identify diagnostic groups suitable now for research projects and other categories that fail this test but have the potential for rectifying by further investment in research. Methods Data were collated via a questionnaire completed by the referring clinician at the time of notification. Analysis provided accurate diagnoses in 3 categories: defects in testis determination, defects in androgen production and defects in androgen action. Genetic analysis was then targeted to sequence 5 genes: 17HSDB3, SRD5A2, AR, SRY, NR5A1. Results The following yield was obtained: 17 beta HSD deficiency (n=30), 5 alpha RD deficiency (n=45), complete androgen insensitivity syndrome (CAIS) (n=239), partial AIS (PAIS)(n=59), all proven by demonstrating pathogenic mutations. In the testis determination category (gonadal dysgenesis, n=73), SRY and NR5A1 mutations were detected in 14 and 6 cases, respectively. A further 390 cases with a phenotype predominantly similar to PAIS or possibly partial gonadal dysgenesis remain incompletely characterised. Discussion A large database when mined using comprehensive information has successfully identified a large proportion of the causes of XY DSD. This provides an excellent resource for further studies such as outcome in adulthood, including effectiveness of hormone replacement and risks for germ cell tumours. Less successfully mined is a large, less well characterised group without a DSD cause which would be ripe for analysis by newer genetic techniques, when phenotypic data are better gathered. The DSD professional community across a range of disciplines is challenged to utilise such database resources for further studies.

O-12 Birgit Köhler

dsd-Life: Clinical European study on the long-term effects of hormonal and surgical therapy and psychological intervention in disorders of sex development (DSD)

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Background: Since the last two decades the genetic causes and the pathogenesis has been identified in many cases of DSD. However, clinical practice as decision on the sex of rearing, genital surgery and hormone therapies has a life-long impact on the affected persons and evaluation of long term outcome for clinical care is needed. Previous clinical outcome studies of DSD were limited by small patient numbers, different outcome measures and conglomerates of genetic defects. dsd-Life is a large and comprehensive outcome study integrating all medical and psychosocial issues to improve treatment and care of DSD. Objective: The aim of dsd-Life is improvement of clinical care of patients with DSD and development of European guidelines for clinical care of DSD. Moreover, dissemination of general knowledge about DSD to the public will be enhanced through the project. Methods: dsd-Life is a European study evaluating the long-term effects of hormonal and surgical therapy and psychological intervention in the different genetic entities of DSD: sex chromosome DSD (including Turner and Klinefelter syndrome), XY DSD and XX DSD. Different areas of high importance for long-term well-being will be evaluated: quality of life and psychological well-being, psychosexual development, metabolism and health. Patients'/parents' view, ethics and cultural context will be considered. The dsd-Life project consortium consists of 15 European multidisciplinary DSD teams with longstanding experience in treatment and care of DSD. The consortium includes European DSD specialists in the fields of endocrinology, psychology, surgery, andrology, urology, gynaecology and ethics. dsd-Life communicates and collaborates closely with different national patient support groups. The recruitment of participants will start in October 2013 and will be performed by the study centres, associated hospitals, patient support groups and I-DSD. DSD-Life is a EU project (FP7/ 2007-2013). Funding 2012-2016. Coordination Dr. Birgit Köhler, Charité Berlin.

O-13 Rod Mitchell

Modeling Testicular Dysgenesis and Endocrine Disruption in the Human Fetal Testis

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Background: Male reproductive disorders (cryptorchidism, hypospadias, testicular germ cell cancer, low sperm counts) comprise a 'Testicular Dysgenesis Syndrome' (TDS) with a common origin in fetal life. These abnormalities also occur in many of the Disorders of Sex Development (DSD). A variety of genetic and environmental (endocrine disruptors) factors are proposed to play a role in the aetiology of these disorders. Clear differences exist between rodents and humans in terms of testis development and dysgenesis and therefore human relevant models are required. Objective: 1) Establish models of ex-situ human fetal testicular development to investigate seminiferous cord formation/disruption. 2) Determine the effects of proposed endocrine disruptors on the developing testis. Methods: We xenografted testis tissue/cells from fetal human (9-20 wks, n=21) or rat (e17.5, n=39), into nude mice. Morphological and immunohistochemical analysis was performed to investigate seminiferous cord formation/re-formation and cellular development. In addition, we treated host mice with a variety of proposed endocrine disruptors (paracetamol, phthalates or diethylstilboestrol) or vehicle. Testosterone production and the effect of exposure on testis development were determined. Results: Second trimester human fetal testis xenografts developed normally during the grafting period. Exposure to paracetamol during the grafting period resulted in a significant reduction in testosterone production, whilst exposure to di-n-butyl phthalate or diethylstilboestrol did not, in contrast to exposure in rats where all three result in a

reduction in testosterone. First trimester human fetal testis xenografts formed seminiferous cords during the grafting period, whilst xenografts of fetal rat isolated cell suspensions re-formed seminiferous cords with normal morphological appearance. Conclusions: We have demonstrated models of fetal testis development that can be invaluable for investigating seminiferous cord formation and its disruption in DSD/TDS. We also demonstrate the effects of exposure to proposed endocrine disruptors in the human fetal testis and highlight important differences from those seen in rodent studies.

O-14 Capucine Hyon

Refining the sex determining region located upstream from SOX9 gene.

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Background: Most 46,XX testicular DSD cases carry the SRY gene, usually on one of their X chromosomes. In SRY-negative 46,XX testicular DSD rare genetic causes include mutations involving RSPO1 and WNT4 genes and rearrangements at the SOX9 and SOX3 genes. Recently, two families were reported with 46,XX testicular DSD carrying a duplication or a triplication of a region located about 600kb upstream from SOX9 (17q24). A further study defined a 78 kb region associated with either 46,XX DSD and 46,XY DSD when duplicated or deleted respectively. Aim: The aim of our study was to identify new regions involved in 46,XX SRY-negative DSD, and to define precise genotype-phenotype correlations. Methods: Two phenotypically normal brothers, initially referred for infertility, were shown to carry a 46,XX, SRY-negative, karyotype. They were then analyzed using the Illumina SNP array in order to identify potential deletions or duplications that could contribute to their phenotype. In addition, a testicular biopsy was obtained for each brother. Results: The two brothers carry a 77 kb duplication located 600 kb upstream from the SOX9 gene. Their duplication overlaps the critical region involved in SOX9 gene regulation in the developing gonad. The duplication was confirmed by independent qPCR analysis. Gonad histology revealed a normal seminiferous tubule organization. Ovarian tissue was not observed. Discussion: This duplication is the smallest one reported to date and defines the minimum region associated with DSD to a 64 kb interval, which includes three highly conserved regions. These latter could contain one ore more gonadal enhancers of SOX9 responsible for testicular differentiation when duplicated. Furthermore, the normal male external differentiation and the lack of Müllerian remnants suggest a functional endocrine testis secretion during the prenatal period.

O-15 Jolanta Slowikowska-Hilczer

Preservation of Dysgenetic Gonads - Clinical Outcome

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Aim of the study was to evaluate pubertal or adult patients with Y chromosome and ambiguous genitalia because of gonadal dysgenesis (GD). We evaluated 42 patients with GD, aged 15-46 years, with 46,XY (78.6% of cases), or mosaic karyotype. Serum levels of FSH, LH and testosterone were determined. Ultrasonography of gonads was performed. Preserved gonads were biopsied or removed. In total 83 gonads were histologically evaluated, including immunohistochemical reaction with monoclonal antibodies against placental like alkaline phosphatase (PLAP), a marker of neoplastic germ cells. Morphometry of testicular structures was achieved with the use of image analysis software. In all patients serum FSH level was increased above 10 IU/L (mean 63.7±38.3 IU/L) and volume of gonads diminished (<10 ml). In 71.5% of patients serum testosterone level was below 8 nmol/l (mean 5.1±3.9 nmol/L), LH increased above 10 IU/L (22.1±12.7 IU/L) and they had clinical symptoms of hypogonadism. Germ cell neoplasia was found in 30.1% of gonads. Among them overt germ cell tumours were revealed in 10.8% of cases. In gonads with testicular structure intratubular germ cell neoplasia predominated (47.2%), while in the streak gonads gonadoblastoma (26.7%) was the most frequent. In one case spermatozoa were found, in one spermatogenesis was arrested at pachytene spermatocytes level and in another one at the level of spermatogonia. Sertoli cell only syndrome was found in 5 gonads with testicular structure (26.3%) and in one gonad seminiferous tubules were totally degenerated. Testicular structure revealed features of poor organogenesis: diminished tubular diameter, increased thickness of tubular membrane and increased intertubular spaces. In conclusion, dysgenetic gonads preserved until adulthood have poor growth and minimal probability to produce complete spermatogenesis. Moreover, they exhibit high risk of germ cell neoplasia. They have also poor hormonal activity, thus most of patients develop hypergonadotropic hypogonadism.

O-16 Yvonne van der Zwan

Chromatin profiling of germ cell cancer cell lines reveals differences in active enhancer states between Seminomas and Non-seminomas: a GENVIRONMENTAL connection?

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Background Interplay between (epi)genetics and environment is involved in formation and maintenance of normal gonadal development. Primordial germ cells (PGCs)/gonocytes undergo specific epigenetic modifications. A disturbed micro-environment during this process might result in disturbed fertility and malignant transformation. Germ cell cancers (GCC) are the most common

cancer in young men, originating from PGCs/gonocytes, and are subdivided into seminomas (SE) and non-seminomas (NS). Somatic mutations are rare in GCC, therefore it is hypothesized that epigenetic disregulation might be involved. As such, investigation of histone modifications could be informative to elucidate the mechanisms involved in the formation of GCC, and might identify markers for risk stratification, diagnosis and prognosis. Aim Gain insight into the role of histone modifications in development of GCC. Methods We studied two well characterized GCC-cell lines, TCam-2 and NCCIT that are representative for SE and NS, respectively. Chromatin immunoprecipitation analysis was performed, using antibodies against three histone modifications; H3K4me1, H3k4me3 and H3K27ac. Libraries from the enriched DNA were prepared, and sequenced on the SOLiD 5500xl sequencer to generate genome-wide profiles. Results We identified a defined pattern of active regulatory regions within the genome, including promoters and enhancers. Initial analysis matched the classification of the cell lines; SOX17 was strongly enriched for H3K4me1 and H3K27ac in TCam-2 compared to NCCIT cells, whereas the opposite pattern was observed for SOX2. Detailed investigation of the epigenetic differences, in both the cell lines and primary GCC samples, is ongoing. Conclusion We generated a database of the epigenetic constitution of representative cell lines for the major variants of GCC, SE and NS. Extensive analyses, and confirmation of primary patient samples, is expected to give novel insights into the epigenetic differences between SE and NS, and may increase understanding of the maintenance of pluripotency characteristics of GCC, possibly linking genetic and environmental risk factors.

O-17 Anu Bashamboo

Exome sequencing reveals mutations in FOG-2 associated with 46,XY DSD

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Background. The underlying genetic aetiology in the majority of patients with 46,XY Disorders of Sex Development (DSD) is unknown. Aim(s)/Objective(s). The aim of the study was to identify novel causes of DSD using a whole exome sequencing approach. Methods. Following exome enrichment using the Agilent SureSelect V4 Exome Kit, exome sequencing was performed using the Illumina HiSeq 2000 platform at an average coverage of x50. Results and Discussion. We report two cases of 46,XY DSD associated with mutations in the Friend of GATA-2 (FOG2 or ZFPM2) gene. The first individual, who was raised as a girl, carried two missense mutations in FOG2. One was a heterozygous de novo mutation p.R260Q that is located in a highly conserved zinc finger motif. The other mutation, p.M554I was homozygous and inherited from each parent who are second degree cousins. The second individual presented with 46,XY complete gonadal dysgenesis and carried a heterozygous p.S402R mutation. This mutation was inherited from her mother and the family history indicated 46,XY DSD on the maternal side. In both cases ex-vivo functional assays indicated aberrant biological activity for the mutant proteins. These results highlight exome sequencing as a increasingly powerful and cost-effective technique to discover rare genetic variants associated with DSD.

O-18 Martina Rodie

Sexual dimorphism of in vivo rodent brain chemistry using Magnetic Resonance Spectroscopy

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Background: By providing a non-invasive, functional insight, Magnetic Resonance Spectroscopy (MRS) has the potential to provide objective longitudinal data on mammalian brain development. Sexually dimorphic spectroscopy has been reported in humans but not in the rodent model. Aim: To assess the sexual dimorphism in rodent brain chemistry using in vivo MRS. Methods: Male and female Sprague Dawley rats were treated on postnatal days 1-5 with either 50mg/kg flutamide SC or corn oil and then scanned at the age of 6wks and 10wks using a 7TMRI scanner. Metabolites were expressed as a ratio to creatine and full width at half-maximum (FWHM) of the water peak was used as a marker of reliability. Results: Median weight in 6wk control males (MC6) and females (FC6), 6wk treated males (MT6) and females (FT6), 10wk control males (MC10) and females (FC10), 10wk treated males (MT10) and females (FT10) was 176g(range,137-230), 127g(120-140), 177g(133-204), 131g(125-146), 302g(272-365), 205g(180-215), 289g(266-315) and 196g(196-197) respectively. Anogenital distance(AGD) was reduced in MT6 and MT10 when compared with control males(p=0.003,p=0.019). Phallus length was reduced in MT10 (p=0.028). FWHM range was within the optimal range at 12-18Hz. MT6, MT10 and FC6 had higher myo-inositol ratios when compared with control males(p=0.000,p=0.0821,p=0.037). In control males, there was a decrease from 6wks to 10wks in 3 metabolite ratios: GABA(p=0.011), glutamine(p=0.031) and glutamate(p=0.022). In control females there was also a decrease in glutamine and glutamate from 6wks to 10wks(p=0.033,p=0.016). Conclusions: Effects of neonatal androgen blockade are manifested in the male rat as undermasculinisation of the genitalia as well as a brain metabolite pattern which resembles that in the female rat . MRS is a reliable tool for studying the brain in maturing rats and may be a useful tool for studying the link between longitudinal changes in sex steroids and brain metabolism.

Abstracts - Poster Communications

P-01 Angela Lucas-Herald

The Outcome Of Prenatal Identification Of A Sex Chromosome Abnormality

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Introduction: Prenatal diagnosis (PND) via amniocentesis or chorionic villus sampling may result in the identification of a sex chromosome abnormality, often as an incidental finding. Aims: To ascertain the incidence of sex chromosome abnormalities detected by prenatal diagnosis in the Grampian and the West of Scotland (WoS) regions and to determine the characteristics and outcomes of these cases. Methods: Retrospective review of all cases of prenatal diagnoses that revealed a sex chromosome abnormality between 2000 and 2012. Results: Over the period of 12 years, 166 positive cases were identified. The indication for PND was an abnormal ultrasound scan in 95(57%), high-risk first trimester screening results in 31(19%), age related aneuploidy risk in 24(14%), maternal anxiety in 9(5%) and a family history of a chromosomal abnormality in 7(4%). Of the 166 cases, 79(48%) cases were 45,X, 24(14%) were 47,XXY, 14(8%) were 48,XXX, 9(5%) were 45,X/46,XX,, 8(5%) had a structurally abnormal X chromosome, 7(4%) were 45X/46XY, 6(4%) were 48,XYY, 2(1%) were 46,XX/46XY and 17(11%) had other variations of sex chromosomes. Of the 166, 73(44%) pregnancies were terminated and of these cases, 47(64%) had a karyotype of 45,X. An additional 7 pregnancies(4%) were associated with an intrauterine death and 5 of these were 45,X. Based on a combined birth rate of 40,000 births per year for these regions, it is estimated that there was one positive case for 3,500 births and approximately half of these led to a live birth. Conclusions: 1:7000 births are associated with a prenatally diagnosed sex chromosome abnormality. 45,X is the most commonly encountered abnormality. Given the rare incidence, there is a need to improve our understanding of the care of these cases during the pregnancy as well as afterwards.

P-02 Angela Lucas-Herald

Range Of Urinary Steroid Metabolite Ratios In Children Undergoing Investigation For Suspected Disorder Of Steroid Synthesis

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Background: Calculation of a urinary steroid metabolite ratio (uSMR) may be a useful method of improving diagnostic yield when investigating disorders of steroid hormone synthesis. Objective & Hypothesis: To investigate the range of uSMR in children with suspected disorders of steroid hormone synthesis. Population / Methods: Ten ratios were calculated on steroid metabolite data analysed by GC-MS in urine samples collected between 2008-2010 from 219 children who were undergoing investigations. To obtain reference data, urine samples were also analysed in 89 children with no background of endocrine concerns and who had a urine sample collected at presentation to the hospital with an acute illness. Results: Of the 89 reference children, 36(40%)

were male and median age at time of the test was 3 yrs(range,1month-11yrs). Of the 219 endocrine patients, 64(29%) were boys. In 129(59%) cases, a urine sample was collected to investigate early or exaggerated signs of adrenarche. Median age at test was 7.4yrs(1day-18yrs). Median and ranges of steroid ratios used in the diagnosis of 21-hydroxylase deficiency were calculated. Differences were noted in the reference ranges according to age and gender. Conclusions These novel data show that reference ranges for urinary steroid metabolite data need to be age matched. Most children with suspected disorders of steroid synthesis have a ratio which is within the reference range and the identification of outliers will lead to better targeting of genetic analyses.

P-03 Erin Bergner

News Coverage of Disorders of Sex Development, 1993-2012

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Background The news media is a powerful mechanism through which public understandings of medical conditions are created and shaped. Although news coverage can promote awareness about a condition and provide information about appropriate health care (Rowe et al. 2003), news media can also present unbalanced and often non-evidence-based claims about health topics, as seen in research on prostate cancer, depression, schizophrenia, and genetics (Goulden et al. 2011; McKenzie et al. 2007; Petersen 2001). Examining how disorders of sex development (DSD) is depicted in the news media offers insight into a range of clinical issues, including various social aspects of DSD diagnoses. Examining DSD through a lens of a social diagnosis (Brown et al. 2011) uncovers the interplay of broader social factors and individual conditions that affect health. Objectives In this analysis, I identify the range and quality of DSD-related issues discussed in the U.S. news media. I examine which clinical issues are given media coverage and what that coverage looks like, including how particular issues are framed. Methods Articles published between 1993-2012 in four U.S. national newspapers (New York Times, Washington Post, Los Angeles Times, and USA Today) were collected using the keywords “intersex” and “disorder(s) of sex development,” yielding a sample of 106 news articles. Articles were coded for substantive content and themes, including the ways they describe DSD and the clinical issues they address. Results and Discussion DSD-related issues are receiving increasing attention from health advocates and medical professionals. Findings show that news media are also giving increased attention to DSD-related stories, particularly in the last five years. Many focused on runner Caster Semenya. My analysis shows that coverage often employs a biological frame, explaining the chromosomal or hormonal characteristics of DSD conditions. However, aspects of health care and treatment are sidelined.

P-04 Karen Meadley

Neovagina in patients with Mayer–Rokitansky–Küster–Hauser syndrome.

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Background: The diagnosis of an absent uterus and vagina is devastating in view of psychological, social and reproductive issues. The creation of a neovagina should be structural as well as functional to enable the woman have comfortable sexual intercourse. Aim: The aim is to discuss

the pros and cons of different methods available to create a neovagina, with special emphasis on the Mcindoe procedure. These include the low risk non-surgical method using vaginal dilators and the surgical methods consisting of the McIndoe procedure, Vecchietti and Davydov procedures. We present a case among other cases in which the McIndoe procedure was successful. Discussion: The McIndoe procedure is one of the procedures that have been described as out-dated procedures in view of the associated serious risks and complications; with the availability of safer laparoscopic procedures, the British Society for Paediatric and Adolescent Gynaecology recommends that they are not performed in the UK. However, the McIndoe procedure is still being successfully performed in Scotland. This involves the use of a full-thickness skin graft over an expandable foam rubber mould placed in the canal between the bladder and rectum. The use of the full-thickness skin graft reduces the postoperative contraction previously noted with the split-thickness skin graft requiring long-term utilization of a vaginal form, which is undesirable if unnecessary. Recently, it has been shown that a full-thickness skin graft takes as well as a split-thickness graft. The main disadvantages are potential vaginal stenosis, perforation of the bladder and rectum, graft failure and unsightly scarring at the graft site. Vecchietti method and modifications of similar laparoscopic procedure are complicated and technically demanding. All these techniques are associated with discomfort and require a long period for adequate results. McIndoe procedure is simple and the results are reproducible and it remains one of our preferred choices.

P-05 Wiebke Birnbaum

The decision making process in a case of late diagnosed 5a-reductase deficiency

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Background: There is a lack of standardization of medical consult within the field of DSD. New ethical recommendations have to be considered. Objective We describe a case of 5a-reductase deficiency as an example for a complex condition. Our multidisciplinary team was consulted to lead the decision-making process. What are the individually tailored steps to ensure a satisfying long-term outcome? Methods We present a Kurdish 46, XY girl not diagnosed with 5-ARD until the age of 13 1/2 years and sketch the steps which contribute to the informed medical consent. Diagnostic evidence was achieved by molecular genetic analysis. We explained 5-ARD and the specific implications to the patient and the family attended by a translator. The psychologist assessed gender behaviour and identity. Information from the local child protective service completed the picture of her social setting. Results All involved parties shared facts, treatment options and possible outcomes. The “no treatment” option would lead to irreversible virilisation and gender reassignment. The female line would result in gonadectomy and hormone replacement therapy. The profound consequences for the patient, her immaturity and the fathers ambiguity forbid a finalizing decision at this stage. Hormone suppression allowed a limited moratorium to further evaluate gender identity and to empower the patient to consent. A re-evaluation after 12 months showed a 14 year old teenager with masculine habit and outward appearance. She expressed clearly her female gender identity and homosexual orientation. Estrogen replacement therapy under hormone suppression initiated female pubertal development. Conclusions The management of patients with DSD requires care through specialised multidisciplinary centres which analyses the different options and perspectives. This decision takes time and is straining. Disclosure process and informed consent management need to be

standardised in consideration of patient centred care. Following these guidelines a greater compliance with ethical standards will be achieved.

P-06 Sally Tantawy

Analysis of the gene coding for Steroidogenic Factor 1 (SF-1, NR5A1) in a cohort of fifty Egyptian patients with 46,XY disorders of sex development

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Background: SF-1 is a key transcriptional regulator of genes involved in the hypothalamic-pituitary-gonadal axis. Recently, SF-1 mutations were proved as a frequent cause of 46,XY DSD in humans. Objective: To investigate the frequency of NR5A1 mutations in an Egyptian cohort of XY DSD. Patients: Fifty Egyptian XY DSD patients (without adrenal insufficiency) with phenotypic spectrum of complete female external genitalia with/without uterus (n=8), ambiguous genitalia without uterus (n=5), vanishing/atrophic testes (n=10), hypospadias (n=23) and isolated hypoplastic phallus (n=4). Methods: Molecular genetic analysis of NR5A1 coding for the SF-1 gene. Results: NR5A1 analysis revealed 3 novel heterozygous mutations in 3 hypospadias patients. Patient 1; p.Arg62Cys mutation in DBD zinc finger region predicted to result in conformational change of the protein. Phenotype: hypoplastic phallus (1 cm at 1 6/12 years), penile hypospadias, hypoplastic scrotum, bilateral small inguinal testes, low testosterone, inhibin B and AMH, and high FSH. Patient 2; de novo p.Glu121AlafsX25 frameshift mutation producing severely truncated protein. Phenotype: hypoplastic phallus (3.5 cm at 13 years), hypospadias, bifid scrotum, unilateral cryptorchidism, low testosterone, inhibin B and AMH. Patient 3; p.Ala154Thr hinge region mutation predicted to reduce transcriptional capacity of SF-1. Phenotype: hypoplastic phallus (2.5 cm at 4 years), penile hypospadias, descended testes, mildly decreased testosterone, normal inhibin B and AMH. Mutation transmitted from the healthy father. Neither of the 3 patients had Müllerian structures. Seventeen patients (34%) harboured p.Gly146Ala polymorphism. Conclusion: In our Egyptian cohort we have detected NR5A1 mutations in 3 patients with hypospadias, a frequency of 13% compared to 3-5% in European patients (Köhler 2009, Allali 2011). We recommend NR5A1 analysis in XY,DSD with hypospadias and partial gonadal dysgenesis. Early cryoconservation of sperms in affected males is advised for the risk of progressive gonadal failure (Bashamboo 2010, Tantawy 2012).

P-07 Yvonne van der Zwan

Steroidogenic factor-1 mutations: relation with obesity in humans

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Background Steroidogenic factor-1 (SF1) was originally identified as a master-regulator of steroidogenic enzymes. SF1 knockout mice showed adrenal agenesis, complete testicular dysgenesis, persistent müllerian structures, abnormalities in the ventro–medial hypothalamus (VMH) and late–onset obesity. Studies in rodents with lesions of the VMH have shown the role of the VMH in body weight and appetite regulation. Others studied the role of the VMH in obesity in combination with leptin. Defects in leptin signaling cause severe obesity due to diminished weight reducing actions in the brain. Aim To study the relation between SF1 mutations and metabolism including obesity. Methods 5 patients with a mutation or deletion of the SF1 gene were included. Energy intake and expenditure was measured by a dietician and questioned with the NVE questionnaire and the Baecke questionnaire. Sleep pattern was assessed with the SDSC questionnaire. Body composition was determined by a DEXA scan. Hormonal evaluation included an oral glucose tolerance test, day rhythm of cortisol by saliva sampling, and fasting serum concentrations of cortisol and lipids. Results Mean BMI z-score was 1.55 (SD 1.68). For all but one patient the energy intake was lower than the calculated energy expenditure. Fat rate of all patients was higher than the reference value. Protein intake tended to be higher and carbohydrate intake tended to be lower than the calculated need. Fat intake was too high in one patient. Three reported sleep problems. Salivary cortisol day rhythms showed normal values. Impaired glucose tolerance was noted in one patient. Lipid profiles were all in the normal range. Conclusion We first described the relationship between SF1 mutations, metabolism and obesity in humans. Preliminary results show a negative relation; energy intake was lower than energy expenditure and no weight loss was observed.

P-08 Asmahane Ladjouze

Clinical heterogeneity in patients with NR5A1/ SF1 mutations: About four cases of Algerian patients presenting with 46, XY Disorder of sexual differentiation.

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Recently, several heterozygous SF1 mutations have been reported in patients with a wild spectrum of 46, XY DSD. We report the cases of 4 patients from two Algerian families, presenting different degrees of DSD due to SF1 mutations. Patients 1 and 2 were brothers who were referred respectively at birth and 16 months for ambiguous genitalia. They had penoscrotal hypospadias, patient 1 had undescended testes. Their karyotype was 46, XY and their genitography revealed the presence of Mullerian structures. Testosterone basal levels were low with an impaired response to ßHCG. AMH levels were normal in patient 1 but low in patient 2. Analysis of SF1 gene revealed a heterozygous mutation (c.370 del C). The brothers were raised as boys and underwent surgical treatment. Patients 3 and 4 were 20-day-old twins with apparent female genitalia. Patient 3 was referred to our clinic because of clitoral hypertrophy. Pelvic ultrasonography revealed inguinal gonads and a the presence of a Mullerian structure. AMH levels were normal for a male and testosterone increased slightly after ßHCG. Patient 4 presented female "normal" external and internal genitalia and low levels of AMH and testosterone. The karyotype was 46, XY in both sisters. A heterozygous mutation of SF1 (c.938G>A) was identified. They had a normal adrenal function. Patient 4 deceased at 1 year of age because of purulent meningitis. Initially raised as a girl, patient 3 was reassigned as a boy at 18 months because of the pressing request of the parents (after a

good response to DHT gel and a multidisciplinary discussion). Conclusion: These case reports illustrate the phenotypic variability (from complete sexual reversion to isolated hypospadias) of SF1 mutations in patients with 46, XY DSD. The question of the sex of rearing remains sometimes very difficult with a lot of uncertainties concerning those children's future.

P-09 Nadine Christina Diana Hornig

Transcription analysis of APOD and PPAP2B in genital skin fibroblasts derived from male controls and AIS patients

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Background: Androgen insensitivity syndrome (AIS) is a X-chromosomal recessive syndrome caused by partial to complete resistance of the androgen receptor (AR) to androgens in genetically male individuals. While complete AIS is relatively rare (1 in 20,000 live births), partial androgen insensitivity (PAIS) is probably the commonest cause of fetal male underandrogenisation. PAIS ranges phenotypically from ambiguous genitalia, hypospadias to normal genital development in males with infertility. For appropriate counseling, sex assignment and potential prediction of puberty development in PAIS it is crucial to determine the individual residual activity of the AR in response to androgen. We previously identified APOD and PPA2B as androgen target genes in scrotal control tissue, while no upregulation was detected in individuals with complete androgen insensitivity syndrome (CAIS). Aim: We aimed at improving our previously published functional assay on APOD and PPAP2B in order to investigate AR transcriptional activity in primary genital tissue obtained from AIS patients. Methods: Tissue cultures of more than 300 fibroblast cultures from male controls and AIS patients are being planned. We have measured APOD and PPAP2B transcription in the presence or the absence of dihydrotestosterone under optimized assay conditions. Results: Our data confirm that both, APOD and PPAP2B are androgen target genes in normal control fibroblasts. AIS samples show variable patterns of inhibited transcription of these target genes compared to a strong response in male controls. Discussion: Measurement of androgen regulated target genes in genital fibroblasts is of high potential value for the characterization of AR function in individuals with AIS. Transcription analyses of APOD and PPAP2B in the complete cohort of 300 patients, sequence analyses of the AR gene in each sample as well as determination of AR expression are necessary to evaluate the functional role of the two genes as biomarkers of AR function in AIS.

P-10 Marek Niedziela

A novel Q117X SRY gene mutation in a 46,XY girl with Swyer syndrome

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Background: A 13-year-old normal stature girl with osteoporosis and lack of sexual characteristics was admitted to the pediatric endocrine section for diagnostic and therapeutic purposes. Prior basal hormonal data confirmed low estrogen level (17 pg/ml), hypergonadotropic hypogonadism (LH 42.72 mIU/ml; FSH 154.66 mIU/ml) and 25(OH)D3 deficiency (15 ng/ml) and therefore she was referred to the genetic clinic. Routine karyotyping showed 46,XY karyotype with total sex reversal and therefore Swyer syndrome was suspected. Aim:To determine the genetic cause of lacking secondary sexual characteristics with primary amenorrhea in a 46,XY adolescent girl with hypergonadotropic hypogonadism and with a normal renal function Methods: After completing clinical, biochemical, hormonal, genetic and imaging examination, the patient underwent laparoscopic gonadectomy and simultaneously a direct sequencing of the coding sequence of the SRY gene on peripheral blood DNA was performed according to standard procedures. Results: Direct sequencing of the coding sequence of the SRY gene enabled to detect a novel nonsense Q117X mutation. This mutation leads to premature termination of translation and protein truncation in the SRY protein HMG-box and is unequivocally pathogenic. Discussion: It is known that HMG-box binds specifically to the AACAAAG double-strand DNA sequence of the male-specific-genes and in this way regulates their replication and transcription. The critical role in this process is played by Ile168 that is lacking in our patient, so the function of the SRY protein is completely blocked what fits to the total sex reversal phenotype of the patient. Mutations in SRY can lead to diminished expression and function of SRY, resulting in sub-optimal SOX9 expression, Sertoli cell formation and subsequent lack of proper testicular development. Conclusions: This is a new mutation affecting the SRY gene in 46,XY females with sex reversal and this mutation should be considered in genetic counseling.

P-11 Scott Shepherd

One For Dex And Dex For All: Challenges In The Management Of Congenital Adrenal Hyperplasia (CAH) In A Multiple Pregnancy

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Introduction Prenatal glucocorticoid treatment to minimise genital androgenisation in pregnancies associated with CAH remains controversial. The likelihood of multiple pregnancies will increase as more subfertile adults with CAH seek assisted conception. Case The father of the index cases who was subfertile was diagnosed in infancy and required life-long steroid replacement due to a homozygous deletion within the CYP21A2 gene. On screening, his partner had a different heterozygous mutation in the CYP21A2 gene. Following successful assisted conception and

uncertainty about the reliability of prenatal diagnosis in the setting of a twin pregnancy, parents declined prenatal diagnosis but opted for empirical treatment with oral dexamethasone 1.5mg TDS from week 10 of pregnancy until delivery. An early prenatal ultrasound confirmed a twin female pregnancy. Planned caesarean section was performed at 37/40. The birthweight of Twin 1 and Twin 2 was below the 2nd centile at 1.89kg and 1.96kg respectively. On D4, serum electrolytes were within the normal range in both infants but 17-OHP was higher in Twin 1(29nmol/L) than Twin 2(3.4nmol/L). Following an uneventful neonatal period, both twins were discharged home on Day 5. At Day 13, Twin 1 exhibited mild clitoral prominence and had elevated serum androstenedione at 2.7nmol/L and was commenced on glucocorticoid, mineralocorticoid and salt supplementation for presumed CAH. On D13, Twin 2 had a sub-optimal peak cortisol of 283nmol/L on ACTH stimulation but this had normalised by Wk6. Genetic testing confirmed that Twin 1 had a compound heterozygote mutation and Twin 2 was a carrier for the paternal mutation. Discussion This case highlights the special challenges faced by clinicians and parents in the setting of a multiple pregnancy and a clearer pathway for prenatal management needs to be developed for these cases.

P-12 Stefan Riedl

Discrepant biochemical findings in a SRD5A2-mutation-negative patient with 46,XY-DSD showing a 5-a-reductase deficiency-typical urinary steroid profile

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Background: Laboratory diagnosis of 5-a-reductase-II-deficiency (5aRD) is usually straightforward comprising reduced urinary 5-a metabolites, increased T/DHT ratio after hCG stimulation and genetic proof of a SRD5A2 mutation. Aim: We present a 46,XY-DSD patient with discrepant urinary versus serum test results in whom no genetic diagnosis has been established so far, for discussion on a possible pathomechanism. Case report: An externally female-appearing infant, child from healthy and non-consanguineous parents, was diagnosed with 46,XY-DSD in the newborn period. Gonads were localised in the inguinal regions and no female internal structures detected. At 3 weeks T was 1.5 ng/mL and AMH normal at 511 pmol/L. Repeated urinary steroid analyses revealed decreased 5-a metabolites, and fibroblast cultures showed decreased DHT generation capacity, whereas serum T/DHT after hCG stimulation was normal (T 3.1 ng/mL; T/DHT ratio 3.9). Genetic tests for SRD5A2 as well as androgen receptor mutations gave negative results. Explorative cystoscopy and laparoscopy revealed inguinal gonads with dissociated epidydimes, normal deferent ducts, no female internal structures and a 2 cm blind ending vagina, separating from the urethra 1 cm proximal of the opening. The penisoid was slightly enlarged at 1.5 cm. Gonadal histology showed testicular tissue with Sertoli-only pattern. The patient, now 12.5 years-old, has been raised as a girl and entered puberty, LH 0.6 mU/mL, FSH 2.0 mU/mL. No virilisation has yet occurred and no increase in testosterone observed (T 0.03 ng/mL), whereas E2 rose (82 pg/ml) leading to slight breast development (B 2-3). Auxological parameters, apart from overweight, have been normal so far and bone-age within the age-related male range. Discussion:

As far as no known genetic defect has been elucidated, we suspect a hitherto undescribed disorder of the 5-a pathway. The androgen backdoor pathway might play a role.

P-13 Miriam Muscarella

Words that Matter: Improving Medical Conversations and Resources Around DSD for Patients and Families Through Individual Experiences

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Background: Many scholarly works are either critical or unquestioning of medicine's roles in the lives of those with DSDs. Few published works focus on communication between physicians and patients/families by examining diverse and often positive medical experiences of individuals with DSD.
Aim/Objective: This paper seeks to develop new strategies for communication around DSD diagnoses and treatments by freshly engaging individual accounts.
Method: Using thematic analysis of semi-structured interviews with individuals with DSD in Australia, this paper integrates the narratives of people with DSD into strategies for enhancing collaboration and communication for doctors and support providers.
Results: In this qualitative study, seven semi-structured interviews were recorded, transcribed, and incorporated into analysis. Four informants identified as having Complete AIS, two identified as Partial AIS, and one identified as bladder exstrophy/Partial AIS. All individuals discussed experiences of youth, medical care, and disclosure. Emerging themes highlight patient diverse experiences and perspectives concerning: timing and tools for disclosure of DSD, medical treatments, and discussing gender in the context of a DSD.
Discussion: These findings offer additional approaches for communication and care around DSD, focusing on: disclosure in youth and adulthood, medical care, and gender identity in relation to DSD. Findings suggest importance of and strategies for accessible and age-appropriate discussions and resources to supplement patient and family's understandings of karyotype, sex development, and DSD."

P-14 Soara Menabò

46,XX DSD with Prader V virilisation, hormonal "conventional" pattern typical for 21-Hydroxylase deficiency (21OHD), and lack of CYP21A2 mutations.

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Background. 46,XX DSD due to CL-11OHD may mimic a patient with CL 21-hydroxylase deficiency (CL-21OHD). Objective. To diagnose correctly a 46,XX virilised patient normal to CYP21A2 gene analysis. Methods. Conventional RIA and ID-LC-MS/MS measurements, genetic analysis. Patient. The female patient, now 1.6 yrs old, was born at term to healthy parents of Sardinian (Italy) origin.

At birth she showed virilised external genitalia (Prader stage V) with clitoromegaly, urethral meatus at the tip of the organ, complete fusion of labia majora and empty scrotal sac. At 2nd day, 17-OH-progesterone (21,0 ng/ml), testosterone (2.4 ng/ml) and ?4-A (94 ng/ml) were high. The low normal Na (136.8 mEq/L) and slightly high K (5.8 mEq/L) induced to start treatment with Hydrocortisone (15 mg/m2/day) and CL 21-OHD was suspected. Ultrasound and cystography/cysto-vaginoscopy examinations showed normal Mullerian structures and urogenital sinus with regular morphology of the vagina, respectively. Surprisingly, CYP21A2 gene analysis was normal. When two months old, the patient was sent to our Centre for diagnostic work up and surgical examination. ACTH test performed after two days of treatment withdrawal, showed the following basal/stimulated results: cortisol 25.8/28.8 ng/ml, 11deoxycortisol 135.9/187.9 ng/ml, DOC 29.9/29.5 ng/ml, D4-A 4.22/5.54 ng/ml, 17OHP 9.13/8.01 ng/ml, DHEA 21.9/21.6 ng/ml, T 0.52/0.48 ng/ml. The CYP11B1 genetic analysis revealed that the patient is compound heterozygous for the paternal novel putative mutation Q337P (CAG>CCG), and the maternal variation +148 IVS5 C>G, suspected to create a new donor splicing site. After repeated dialogues with parents, at the age of nine months clitoridal-labioplasty was decided. Conclusion. To misdiagnosis as 21OHD patients affected by 11OHD may be more frequent than expected. Diagnostic hormonal markers should more easily assayed trough the new LC-MS/MS methodologies. 17OHP values inappropriate for a CL-21OHD, as in the case presented, should make the suspicion of a different enzymatic deficiency.

Map of University of Glasgow Main Campus

Meeting Venues highlighted

For more detailed map and other maps of Glasgow please see http://www.gla.ac.uk/about/maps/