

Abstracts

Plenary: 10 Years After Chicago – a Look to the Future

Consensus & Community:

Ten years of maturing relationships in research, care, & support

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The ten-year period since the publication of the Consensus Statement matured collaborative efforts in DSD in personal and global directions. It helped to incite work to improve care for affected individuals and families, to build upon the evidence base, and to shift how we work together to better care and support. Situating the session of the past, present, and future of the Consensus, we must reflect on personal and global relationships which foster growth in DSD care, research, and support. Moving forward the ‘shared enterprise’ discussed by Ellie Magritte of dsdfamilies.org in the 2013 I-DSD Plenary Session, we consider how our history can help to transform our present and future relationships among the diverse collaborative of stakeholders in DSD care.

The Chicago Consensus and its consequences

Ieuan Hughes, University of Cambridge

The Consensus was a wide-ranging statement. Has it had any impact or has it joined the ranks of statements that merely wither on the vine? (1).

Impact.... certainly, if only because of a radical change in nomenclature and allied terminology. Thus was born the acronym, DSD, for *disorder of sex development*. The literature shows an exponential increase in usage. What has not been so constructive is a dialogue amongst some social scientists and psychologists to dismantle the constituent components of the DSD acronym, bar the word development. That the medical and scientific community is expected to disown the word disorder as a pathophysiologic phenomenon and not utilise the word sex in defining sex dimorphism has created a disconnect with members of some advocacy groups and non-medical professionals. It is difficult to see how this impasse can be reconciled.

The Consensus recommends management only takes place in centres with a multidisciplinary team. A gaping hole had been identified in psychological services; there is now evidence of improvement, although not universally so. Achieving a diagnosis is a challenge, particularly in XY DSD. Has this improved? A 50% non-diagnosis for XY DSD remains a headline figure, but there is now evidence of a reduction in that figure with the application of NGS. A cautionary note is not to discard the availability of judicious use of biochemical tests to target the likely causative candidate genes.

An immense effort post-Chicago was to develop national and international registries. Already, data show a sea change towards male sex assignment in XY DSD. Such knowledge could not reliably be resourced from a single centre. Indeed, the raison d'être of this I-DSD Symposium is to share the wealth of data created by registries and encourage their further usage. So, has the Consensus statement withered on the vine? Hardly, but it has only been

a catalyst to start the long journey of significantly improving the holistic management of individuals with DSD.

(1) Hughes I. Consequences of the Chicago Consensus: A Personal Perspective. Horm Metab Res 2015;47: 394-400.

Supporting the affected child and family

Caroline Sanders, Alder Hey Hospital, Liverpool

Involving parents in the care of their child with DSD, which includes their inclusion in decision-making about their child, can be difficult for all parties involved. Parents play a critical role in their child's development and we need to consider theories of attachment, parenthood, coping and adjustment following the birth of a child with DSD as well as throughout their childhood.

Parents are very often shocked and bewildered in the early days of having a baby with DSD or immediately following a diagnosis about their adolescents DSD. They have to begin to understand complex information, co-create an adaptive parenting model that is flexible and one which can learn to embrace uncertainty as well as accept that evidence based outcomes are unknown.

As such these parents will become the knowledge translators for their children, they need to learn to manage their own feelings, reconsider their beliefs about sex and gender, build safe social networks and balance cultural and spiritual concerns. During this time parents, children and young people also need to develop confidence in the professionals they encounter.

This presentation will consider parenting across the child's development, the influences on parents as well as celebrating their creativity in how they support their children overtime.

A decade of diagnosing DSD conditions

John Achermann, University College London

The Chicago Meeting in 2005 was useful for reviewing the classification of DSD, but how much progress have we made since then? Changes during this time can be looked at in several ways: what is “new”? What is “hot”? What is “accessible”? And what have I learnt from personal practice? What is “DSD” and what are the benefits (and potential burdens) of making a specific diagnosis anyway – will it change our management or improve quality of life for individuals and their families?

The broad diagnostic categories for DSD have remained the same in the past decade but several new specific molecular causes have been described. These include relatively rare new developmental causes affecting gonad development (e.g. CBX2, MAP3K1, GATA4/FOG2, HHAT), alterations in steroidogenesis including the putative “backdoor” pathway (CYB5A, AKR1C2/C4), or changes especially in ovary development due to copy number variation or signalling (e.g. SOX9, SOX3, RSPO1). In contrast, “hot” changes in

diagnosis in the past decade include the rapid expansion of NR5A1/SF-1 associated conditions, WT1 and partial gonadal dysgenesis, the diagnosis of established conditions in adults with DSD, or an awareness of genital variation associated with different syndromes. Our ability to reach a specific diagnosis can involve a range of different phenotypic clues, biochemical tests, imaging or interventions, and genetic analyses. Phenotypic clues may come from prenatal scanning, genital asymmetry, or associated features. Early FISH and karyotype – essential for rapid sex chromosome analysis – is being replaced in some centres by quantitative PCR and microarrays, though it is not clear this will be quicker or if mosaicism will be detected. The measurement of androgens using LC-MS-MS is an important advance, which may help with accuracy of diagnosis, but is not yet widely available. Similarly, interest in urinary steroid profiling – a technique established many years ago – has increased, although accessibility is still somewhat limited. The role of adrenal tests (in the 46,XY baby) remains unclear. “New” biomarkers of testis such as Insl3 may be useful, whereas AMH/MIS is increasingly accessible, but early tumor markers are needed. Assessing ovarian tissue using stimulated inhibin A and estradiol has been proposed. Imaging (ultrasound, MRI) has improved but has certain limitations, and early laparoscopy and histology might be warranted in rare situations. Finally, the explosion in gene technology has seen more rapid and extensive genetic analysis for copy number changes (MLPA, aCGH) and coding genes (candidate, panels, exomes, genomes) with exciting potential but many considerations.

Future challenges are many and include rapid karyotyping and genetic analysis, new biomarkers (especially for early tumours), and predictors of future outcome. Assessing the influence of environment and epigenetics will be difficult but is likely to be important. Dealing with global disparities in access to diagnostic tests is essential as is keeping a firm perspective on how our efforts will improve things for young people and families with DSD.

Genital construction and its timing

Piet Hoebeke, University of Ghent

No issue is open to more controversy as timing of genital surgery in DSD.

While at the end of the last century early surgery was gold standard approach this has changed dramatically since the beginning of this century. It seems that 'surgery and DSD' has been subject to a pendulum going from early surgery to no surgery or delayed surgery. As in any concept that is subject to a pendulum the truth is probably somewhere in the middle.

After the lecture it should be clear that the evidence for either approach is low or non existing and that both extreme approaches are more based on emotions than on science. Taking patients on the roller coaster of emotions is an unacceptable approach therefore it is time to find the rational approach to this controversy and find an acceptable compromise. During the lecture an attempt to define a compromise will be proposed under the concept of gender neutral surgery. The concept of "gender neutral surgery", which sounds as an oxymoron, is even for surgeons negotiable and is the way to stop the pendulum in a neutral position. No winners or losers in the debate only happy patients, the future individuals born with DSD and their families.

The I-DSD Registry and related networks

S Faisal Ahmed, University of Glasgow

Disorders of sex development are a wide range of relatively rare conditions with diverse pathphysiology. Given their rarity and the need for input from a range of clinical disciplines, the clinical management can be challenging, especially in the more complex cases. This situation is worsened by a lack of evidence for the clinical utility of many diagnostic and interventional procedures. Thus, variation in outcome as well as management is not surprising. By working as a network of clinical and research centres, it is possible that these variations can themselves be better managed and studied. Networks also have the potential to guide research and can act as a conduit to patient and peer support groups. Finally, they can lead to the development of care standards which can guide the creation and long-term sustainability of centres of expertise. Over the last decade, there has been a major shift in the field of DSD towards greater collaboration and networking. The International DSD Registry which was initially supported by the European Society for Paediatric Endocrinology, followed by the EU and, more recently by the MRC, is an example of how a Registry can facilitate and support the development of clinical and research networks whilst acting as a personalised tool for the affected person. This talk will focus on the development of the I-DSD Registry, its current activities and links to DSDnet and its future directions.

Short Oral Communications

Current Models Of Practice & Professional Development Of Clinicians In DSD Centres – Results From An International Survey Of Specialist Care For DSD.

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Background: In the optimal care of children with Disorders of Sex Development(DSD), it is generally considered good practice to work within a multidisciplinary team(MDT) and engage in opportunities for professional development. **Methods:** To explore the current models of MDT practice and the extent of professional development in specialist DSD centres, an international survey of 124 paediatric endocrinologists, identified through DSDnet and the I-DSD Registry, was performed in the last quarter of 2014. **Results:** A total of 77/124(62%)clinicians, in 74 centres, from 38/42(91%) countries responded to the survey. In 61(82%) of the centres, the lead of the team that provided DSD care was a paediatric endocrinologist with the next commonest being a clinical geneticist in 5(7%) centres. The surveyed clinicians responded that the following paediatric specialists would be routinely

involved in the initial evaluation of a newborn - endocrinologist(98%), surgeon/urologist(95%), radiologist(94%), neonatologist(90%), clinical geneticist(81%) and clinical psychologist(69%). However, during the first week after presentation, a team consisting of paediatric specialists in endocrinology, surgery/urology, clinical psychology, neonatology and nursing was only possible in 29/74(38%) of centres. Over the first three months after presentation, a team comprising of paediatric specialists in endocrinology, surgery/urology, clinical psychology, nursing and clinical genetics was only possible in 33/74(43%) of the centres. A nationally organised network or plan for managing rare conditions such as DSD was reported to exist in 14/38(37%) countries. Of the 77 clinicians, 28(36%) kept a local DSD registry only, 40(52%) shared their data in a multicentre DSD registry and 9(12%) did not record any data. Participation in audits/quality improvement exercises in DSD care was reported by 13/74(18%) centres in 6/38(15%) countries. Attendance in local, national or international DSD related educational programs was reported by 69%, 78% and 82% clinicians, respectively. **Conclusion:** Although an increasing number of DSD centres have access to specialist staff, the actual delivery and quality of care provided by these staff requires further exploration. Professional development and engagement in activities that may lead to improved care need further attention.

A Web-Based Tool for Shared Decision-Making in DSD

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Background: The birth of a child with DSD is anxiety-provoking. Stressors associated with ascertaining a DSD include weathering drawn-out diagnostic testing periods, absorbing complex medical information, and managing strains on family and other social relationships associated with potentially stigmatizing conditions. It is in this context, when usual social support systems are often perceived as inaccessible, that parents are called upon to make decisions having pervasive consequences for their child. Decision support tools (DSTs) are designed to facilitate patient involvement in decision-making by identifying decision points, delivering information about options and outcomes, and clarifying personal values. DSTs complement, rather than replace, counseling from healthcare practitioners.

Objective: We describe, here, the first attempt at creating a web-based DST for DSD.

Methods: In *Phase I*, an online DST was created following *International Patient Decision Aid Standards* guidelines and revised in an iterative manner following input on content and functionality from healthcare providers, patient advocates, and parents of affected children. In *Phase II*, healthcare providers at three US medical centers audio-recorded the earliest provider-family discussions (n=15 index cases) and subsequent consultations about

diagnostic findings and treatment options. Parents completed questionnaires about psychosocial adaptation and decision-making, and a semi-structured interview.

Results: Topics identified by stakeholders, and included in the DST, include: gender assignment, genetic testing beyond karyotype, and decisions regarding gonads, genital surgery, sharing information with their child and others. The interactive DST is intended to help parents make intentional choices among options by providing information relevant to their child's DSD and addressing emotional states and values that inform their decisions. The study is now ready to move into *Phase III*: introducing the DST into usual care. Comparisons of *Phase II* vs *III* audio-recorded provider-family consultations, parent-report questionnaires, and interviews will serve as additional outcome data.

Conclusion: The presentation delivers an overview of the DST, strategies for introducing the tool in varying referral contexts (e.g., NICU consultation, patient transferred from other hospital) and DST evaluation strategy.

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Congenital adrenal hyperplasia (CAH) in Melbourne: Surgical timing and complications, with outcomes including body image and genital sensation in a cohort study

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Background

CAH in females is associated with virilisation in utero. Feminising genitoplasties have been offered as part of routine care for many years, although considerable debate now exists relating to concerns regarding complication rates with early surgery, poor outcomes, need for further surgery, and lack of involvement in decision making by the affected person.

Methodology

All patients who had undergone their first feminizing genitoplasty related surgeries at Royal Children's Hospital(RCH) had their records reviewed(n=80) for Prader staging, age at time of surgery, operation and complications.

Followup was attempted for all RCH female CAH patients aged 12---40 years(n=71). Contact was established with 43 women. Five declined participation, 23 completed 1 or more study components, and 15 failed to complete the study. Questionnaires and assessments were undertaken, including genital sensation tests and questions on body image and the persons perspective regarding their surgery. Controls were women of same age attending well womens clinic.

Results

Mean age at surgery was 15 months. Operative complications: 1 serious and 2 minor complications identified, with no correlation to age of surgery. Only 1 of the 10 patients who underwent repeat surgery required significant surgery. Standardised genital sensation assessment [CAH(n=8), and controls(n=11)] :---no difference in vibration; light touch revealed marginal increased sensation in CAH women, but otherwise with no difference in reported sensation.

Of 25 women with CAH who answered body image questions, their concern was their genitalia(n=3), obesity(n=10), steroid effect on face(n=1), hirsutism and pigmentation(n=3). In the 19 control women, weight and stretch marks(n=9), skin problems(n=3). No significant differences in responses.

When asked specifically about body image related to their genitalia: CAH population responses were: 16/20 no concerned, clitoral size(1), labial colour(1), excess labial skin(1), nonspecific concern(1). For controls:(n=19), one was mildly concerned(Fishers exact ns difference).

When women with CAH were asked about timing of their surgery, 15/21 felt early surgery was good; 4 said their surgery was 'too late'(of these, ¾ first attended RCH in adolescence); 1 each reported surgery was 'too early', 'don't know'.

Conclusions

The complication and reoperation rates were low. Outcomes including satisfaction with surgery timing, body image and sensation was high.

The Scottish Audit of Atypical Genitalia

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Background: The early management of atypical genitalia has been highlighted as being of critical importance in the UK DSD Guidance issued in 2011. Our aim is to estimate the incidence of atypical genitalia in Scotland requiring early specialist input in neonates, and to study its clinical presentation and management.

Methods: Prospective ongoing audit through the Scottish DSD network and the Scottish Paediatric Endocrine Group, between June 2013 and March 2015. Monthly emails were sent to clinician members to notify newborns ≥ 37 wks gestation with atypical genitalia requiring specialist input in the previous month and who were aged <4 wks at presentation. Notified newborns were followed up to 3 months age. Cross verification through regional genetics laboratories was performed using karyotype as a marker to identify newborns with suspected DSD.

Results: Over this 21 month period, 32 newborns were reported, of whom 21 were true positives. In addition, 3 extra cases were identified through the cytogenetic laboratories. Amongst the 11 false positives, 4 were born at gestation <37 wks. The incidence of atypical

genitalia requiring specialist input within the first month of birth, in term newborns in Scotland was calculated at 1 in 3232. Of the 19 cases who completed the 3month follow-up, 12(63%) presented within 24hrs. Age at sex assignment ranged from birth to 4 days with the majority, ie 11(58%), having sex assignment at birth. No cases of sex reassignment were recorded. 11(58%) were assigned male sex with XY karyotype. Of the 8 girls, 3 were XY. Neonatologists, endocrinologists and urologists were mostly involved and communication between health care professionals and parents was mainly through face to face discussion.

Conclusions: Atypical genitalia requiring specialist input and investigations within the first month of life is rare and occurs in about one term newborn in every 3232 born in Scotland. Electronic targeted surveillance of members of closely collaborating networks can be beneficial for assessing the early management of conditions presenting as DSD.

Well-being of people with an intersex condition – a qualitative study on experiences with medical care and quality of life.

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Background

Previous studies have shown that long-term quality of life (QoL) may be impaired in people with an intersex condition/DSD. Recognizing that the origin of this impairment is often multi-factorial and that medical care in the past has both improved and worsened QoL in this group, further understanding of personal experiences is valuable.

Methods

Data collection was part of the DSD-life study (www.dsdlife.eu). At the VU medical center site (Amsterdam), semi-structured interviews on QoL and experiences with care were performed by the author. In a nine month period 52 individuals participated, with an age ranging from 18 to 74 years (including both XY DSD (n=27), Klinefelter syndrome (n=17), CAH (n=5) and Turner syndrome (n=3) diagnoses).

Results

Although some determinants were condition-specific, QoL of people with an intersex condition may be conceptualized in a biopsychosocial framework (figure 1). Biological factors included infertility, outcomes of surgical interventions or secondary medical issues. Often mentioned psychological factors were identity stress, body image, and the worries of being an inadequate partner. Despite being less considered within the biomedical discourse, social factors were commonly reported. Both micro- and macro social factors were distinguished. The first may include supportive partner- and parental-relationships and sexual enjoyment. The latter included internalized views of normality in the medical field and society. Often mentioned demands for improvements of care were the establishment of structured and integrated care for adults, more attention for sexual function and for the effect of sex hormones on psychological well-being. Furthermore, respondents mention that

care should always be tailor-made regarding phases of life, partner status, cultural background etc. Finally, information disclosure to others was an often recurring and sensitive topic. Some respondents saw a role for healthcare professionals in informing the general public, and in helping individuals with the process of finding the discourse or protecting privacy.

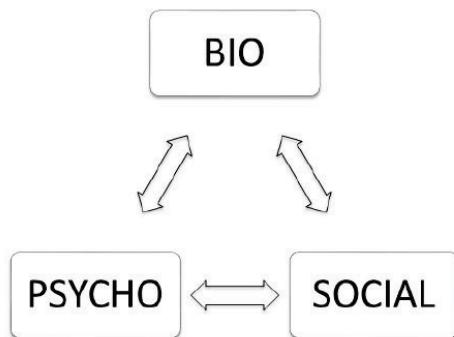


fig. 1: biopsychosocial approach of well-being in intersex

Conclusion

As well-being of people with an intersex condition may be viewed from a biopsychosocial perspective, interdisciplinary care is most often appreciated. A qualitative study design can help identifying relevant future research questions.

GENDER IDENTITY OF PREDICTION IN OLD AGE BY HTP TEST (HOUSE-TREE-FAMILY) IN SUBJECTS WITH DDS 46, XY

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BACKGROUND: Individuals with DDS 46, XY present conflicts and issues related to gender identity. Sex change is not rare among these individuals. The HTP test is a projective psychological test that allows for checking aspects related to sexual identity, social aspects and individual psychodynamic aspects.

OBJECTIVES: To assess gender identity in patients with DDS 46, XY followed at our service through the application of HTP test and compare the results of this test among individuals who maintained the social gender in adult life with those who didn't.

RESULTS: We performed the HTP test in 95 subjects with DDS 46, XY. For analysis purposes, we considered appropriate when the test result matches the social gender and inappropriate when it doesn't. We compared the adjustments among individuals who changed and those who didn't change the social gender in relation to childhood appearance and adulthood appearance (after the change in who underwent change) as well as in relation to their psychosexual identity. We had 20 cases of patients who changed their social gender and 75 who didn't. We noticed that, as for childhood appearance, 100% (20/20) of those who had changed displayed inappropriate HTP (ie had male identit (M) whereas their social gender was female (F) and vice-versa). Among those who did not changed, 74.7% (56/75) were adequate and 25.3% (19/75) were inadequate. As for adulthood appearance 100% of those who changed (20/20) displayed adequate HTP and 93.3% of those who didn't displayed adequate HTP (70/75). As for psychosexual identity,

evaluated after treatment, 100% of those who changed displayed suitable HTP for social gender and 79% of those who didn't change presented adequate HTP.

CONCLUSIONS: The HTP test proved to be a useful tool to assess gender identity. Considering the results obtained it can be said that patients with DDS 46, XY that changed their social gender in adulthood presented that identity since childhood, as demonstrated by their inadequate HTP in relation to their childhood image. Sex change allows these individuals to have an identity according to their gender, as demonstrated by the HTP test performed after treatment.

From Knowing Nothing to “Knowing-now”: Experiences and Expertise among Parents of Children with CAH

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Background

Recent studies with parents of children with atypical sex development and/or CAH have focused on the emotional challenges parents experience around the time of diagnosis as well as the need for better information and involvement in decision-making. In one study, for example, Boyse et al (2014) suggest that having accurate and relevant information gives parents power to cope with the various challenges that they face. However, few studies have explored how the information parents receive is used in practice.

Results

The aim of the present study is to investigate the experiences of parents with children who have congenital adrenal hyperplasia (CAH). The study focuses on the challenges highlighted and navigated by parents as they cope with a child's medical condition and receive support from others, such as health professionals and people in their social network. Semi-structured interviews were conducted with twenty parents (16 mothers and 4 fathers) who had a total of 22 children (16 girls and 6 boys, aged 1-20 years, mean age 9,1) with CAH. Most of the children had salt-wasting CAH. Eight interviews were conducted in the UK and twelve were conducted in Sweden. Interviews were analyzed using a narrative analysis focusing on how challenges, coping and support were experienced over time, from birth to the present.

Conclusions

The analysis suggests that the conceptualization of “information” in the clinical literature on information-giving fails to capture aspects that are important for parents' ability to use information to cope well and to act appropriately. Instead of focusing solely on receiving such information as medical facts (information that can be understood as “knowing that”), parents in this study highlight the importance of knowing what to do with information (a sense of “knowing how”) and when to use their new knowledge in specific situations (a sense of “knowing now”). These interview findings illustrate how parents are required to

build the day-to-day expertise needed for parenting a child with CAH, and suggest how multidisciplinary teams can support parents in this process.

Unraveling embryonic testicular pathways via SOX9 KO RNAseq and SOX9 ChIPseq

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Disorders of sex development (DSD) are a broad spectrum of disorders that can occur at the chromosomal, gonadal or anatomical level. Failing to understand the aetiology of DSD can lead to irreversible clinical interventions, cancer, infertility and psychosocial problems. For majority of DSD cases, the underlying genetic aetiology remain unknown. SOX9 is the central hub gene of male sex determination, which orchestrates the differentiation and function of the differentiation and function of multiple testicular cell types. Misexpression of SOX9 causes DSD (46, XY DSD, 46, XX DSD) in humans, and sex reversal in mice. Here, we have analysed the transcriptome of *Sox9*KO mouse gonads at embryonic day 13.5 in an intact Sertoli cell environment in order to identify genes that are responsive to SOX9. To uncover functionally relevant genes that are direct targets of SOX9, we overlaid the RNA-seq with E13.5 SOX9 mouse ChIP-seq. Our findings suggest that there are several categories of genes that are regulated by SOX9 during male sex development: (a) activated genes/ direct regulation (b) activated genes/ indirect regulation (c) repressed genes/ direct regulation (d) repressed genes/ indirect regulation (e) SOX9 bound genes that are unchanged in *Sox9*KO. In order to discover genes that promote testis development, we focused on the 2938 genes that were > 2-fold down-regulated in the *Sox9*KO gonads. 747 of these genes were bound by SOX9 in the Chip-seq, revealing functionally responsive SOX9 target genes during embryonic testicular development. To narrow down to a set of genes that are SOX9 targets during sex determination, the E13.5 genes were overlaid with the E12.5 SOX9 ChIP-chip dataset of Li *et al*(2014), which revealed 105/747 direct target genes. The top candidate genes will be characterized *in vitro* and *in vivo* to determine their function during male sex development. Further evaluation of candidates includes a) knockout mouse phenotypes; b) OMIM phenotypes and c) design of CRISPR mutants. Genes that prove most promising will be included in a DSD diagnostic assay. This study has the potential to move us from an era where gonadal disorders were defined by histopathology, to one where identifiable genetic mechanisms aid in patient diagnosis.

A tale of two sisters

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Background

Frasier syndrome (FS) is a disorder of sex development (DSD) caused by germline intronic mutations of the Wilms' Tumor (*WT1*) gene, a gene that is critical for normal genitourinary development and renal function. People with FS classically have a 46,XY karyotype, gonadal dysgenesis, female phenotype, focal segmental glomerulosclerosis which progresses to end-stage renal disease (ESRD) in the second decade, and a high risk for developing gonadoblastoma. Inheritance is believed to be autosomal dominant, most cases arising from *de novo* mutations. There are rare reports of FS in siblings, including 46,XX females, in whom parents were asymptomatic, raising the question of possible germline mosaicism. We report sisters with FS who provide further evidence for germline mosaicism, highlighting implications for psychosocial and genetic counseling in FS.

Case Report

A 15-year-old girl presented to our DSD clinic with absent puberty and primary amenorrhea. She had had longstanding proteinuria which progressed to ESRD in adolescence, and was awaiting renal transplantation. She was found to have a *WT1* heterozygous KTS splice mutation, IVS9+4C>T, confirming the diagnosis of FS. Gonadectomy revealed gonadal dysgenesis with unilateral multifocal gonadoblastomas. Although she was accepting of her diagnosis and started on estrogen replacement, counseling for her DSD was complicated by her ESRD and social factors. Subsequently, her 13-year-old prepubertal sister also developed ESRD confirmed to be due to the same *WT1* mutation, and was found to have 46,XY karyotype and bilateral gonadoblastomas. Counseling of the sister was difficult, and she refused estrogen replacement. *WT1* testing of mother was negative, and testing of father was not possible due to his death at age 37 years.

Conclusions

These sisters provide supporting evidence for germline mosaicism being a mode of inheritance in FS. Should this be the case, this raises the important question of whether asymptomatic family members, including offspring and 46,XX females, in FS families should be tested. Our family highlights challenges in optimizing medical and psychosocial management in this condition, despite interdisciplinary care by DSD and transplant teams. Early diagnosis through screening would facilitate counseling, better adjustment, timely hormonal treatment, early tumor management, and better care of FS families.

5α-reductase-2 deficiency: clinical findings, endocrine profile and genetic features in 25 persons

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Background

The 5α-reductase-2 (5α-R2) deficiency is a rare 46,XY disorder of sex differentiation caused by mutations in the 5α-R2 gene. Optimal diagnostic and clinical management is not well definite as well inferences of genotype on phenotype.

Patients and methods

Retrospective records of persons in whom a diagnosis of 5α-R2 deficiency was established in our Departments were reviewed and the clinical, endocrinological and genetic data analyzed.

Results

A total of 25 individuals with certain diagnosis of 5α-R2 deficiency was collected (age at first clinical observation 0.4 ± 1.0 years). About 50% had a misdiagnosis before our observation. Mean period from first observation to definitive diagnosis was 9.1 ± 10.8 years (range 0.1 to 47.0 years); in 8 subjects, gonadal removal was performed before certain diagnosis. Initial sex assignment was female in 16/25 (64%) and male in 9/25 (36%). After diagnosis of 5α-R2 deficiency, sex re-assignment was performed in five babies: 4 girls to male sex and 1 boy to female sex. Baseline testosterone/DHT ratio was diagnostic in 6/12 subjects (first months of life, n = 4; puberty, n= 2), while post-hCG T/DHT ratio was diagnostic in all tested patients by setting the cut-off value at 15 or lower; the peak cut-off of 17 and 30 missed 3 (sensitivity 77%) and 7 (sensitivity 54%) individuals, respectively. 18 different mutations in 5α-R2 gene were identified (homozygous 12/25; compound heterozygous 11/25; monoallelic missense mutation 1/25; homozygous V89L variant associated with high progestin administration during pregnancy 1/25). Five mutations have never been reported (p.G13D, p.P79L, c.281+1G>A, c.331_332delCT, p.V124D). In some individuals, the same mutations were associated with different phenotypes.

Conclusions

This series indicates that consistent time-lag may persist before the diagnosis of 5α-R2 deficiency is established. Sex assignment and gonadal removal may be done before certain diagnosis. Sex re-assignment is usually to male sex, but the contrary may occur. Accurate endocrine evaluation is recommended, since the use of appropriate cut-off values of T/DHT ratio may permit to select individuals with 5α-R2 deficiency. Large genetic variability is present and a clear genotype-phenotype correlation is lacking.

Reducing Uncertainty: Exome Sequencing for the Diagnosis of 46,XY Disorders of Sex Development.

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Disorders of sex development (DSD) have historically been difficult to diagnose, especially at the genetic level. In particular, for cases of 46,XY gonadal dysgenesis, once variants in *SRY* and *NR5A1* have been ruled out, there are few other single gene tests available. Similarly, patients with a working diagnosis of Partial Androgen Insensitivity rarely receive a diagnosis, although knowing the exact etiology of the condition could dramatically influence management.

We used exome sequencing followed by analysis with a list of all known human DSD-associated genes to investigate the underlying genetic etiology of forty 46,XY DSD patients who had not previously received a genetic diagnosis. We were able to identify a likely genetic diagnosis in more than a third of cases, including 22.5% with a pathogenic finding and an additional 12.5% with likely pathogenic findings. In addition, 15% had variants of uncertain clinical significance (VUS) that may be reclassified as literature evolves.

Exome sequencing allowed a remarkable level of genetic diagnostic success in this cohort, especially considering that, for most patients, all other endocrine and genetic testing had been exhausted. Early identification of the genetic cause of a DSD will in many cases streamline and direct the clinical management of the patient, with more focused endocrine and imaging studies and better informed surgical decisions. In the patients with "PAIS", we found mutations in 4 different genes, only one of which suggested true androgen insensitivity. Thus obtaining an early genetic diagnosis was critical to optimal management of these patients.

In addition to searching for variants in all known DSD genes, when exome sequencing is performed on a "trio" with the proband and the unaffected parents, there is the additional possibility of identifying novel genes that will further enhance our understanding of these complex conditions and allow for better care and prognostic information for patients and their families.

Morphological Characteristics of the Gubernaculum in Undescended Testes

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Background The pathogenesis of congenital undescended testis (UDT) still remains unclear. The gubernaculum connects the testis to the inguinoscrotal region and the abnormal attachment of the gubernaculum is the most common operative finding in UDT. In this study, it is aimed to show the morphological characteristics of the gubernaculum in patients with UDT.

Materials and methods Thirty gubernacular tissues are obtained from 25 boys who underwent orchidopexy. The proximal (testicular) and distal (inguinal/proximal scrotal) parts are labeled with division of the excised gubernaculum into two pieces. The specimens are underwent immunohistochemical staining and light- and electronmicroscopic evaluation. Estrogen and progesterone receptor staining, myogenesis, Ki-67 staining of the whole gubernaculum are done. The fibroblastic activity, presence of immature capillary profiles, presence of intermediate filaments and presence of transport vesicles (as a marker of angioneogenesis) in proximal and distal parts of the gubernaculum are compared. The results are analyzed and compared with scoring and Mann-Whitney-U test.

Results It is shown that the whole gubernaculum is a collagen rich tissue with high fibroblastic activity. No myogenesis, Ki-67 staining, and no estrogen and progesterone receptor staining are found. Excessive amount of capillary development in both proximal and distal localization is found. Increased fibroblastic activity, increased immature capillary profiles and excessive intermediate filaments and transport vesicles suggesting angioneogenesis are significantly found in proximal part, in comparison to distal gubernaculum ($p<0.05$). The location of the UDT did not change the results.

Conclusion This study shows that the proximal and distal parts of the gubernaculum have different morphology and cellular dynamics. Whether these characteristics can be compared with the gubernaculi of descended testes, and the if such these findings can explain a step in the mechanism of testicular (un)descensus remains to be elucidated-likewise the etiology of UDT.

Ovotesticular disorders of sex development Surgical diagnosis and management of 32 cases

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BACKGROUND:

Ovotesticular disorder of sex development (OT-DSD) is defined as the simultaneous presence of both testicular and ovarian tissue in the same individual. It is considered the least common and least understood variant of DSD in humans.

PATIENTS AND METHODS:

Thirty cases with OT-DSD were diagnosed and surgically managed in Cairo University-Pediatric Hospitals over a period of 30 years (1984 – 2015). Their ages ranged between one month and 17 years with a mean of 3.8 years. After full clinical examination, cytogenetic, hormonal and radiological studies were accomplished, abdominal exploration with gonadal biopsies were performed via open surgery in the early phases of the study (till 1990) then laparoscopic approach became the standard approach afterwards. Surgical reconstruction was performed as a one-stage procedure in most cases including various techniques for genitoplasty, excision of contradictory internal genitalia, or tumors and surgery for gynecomastia.

RESULTS:

Genital ambiguity with predominance of the male phenotype was the most frequent complaint (77.7%) followed by gynecomastia in 14.8% and inguinal mass in 7.4%. Twenty one patients were raised as males at the time of presentation due to the relative average size of their phallus. The most frequent karyotype was 46,XX in 77.68% of patients, followed by 46 XO/XY, 46XY and 46XX/XY while SRY was negative in all 46,XX. The prevalent gonad was ovotestis (OT=37. %), followed by ovary (OV=as females at the age of 1.25 and 3 years, while one case reversed the sex to male at the age of 2 years. Two male patients developed dysgerminoma and gonadoblastoma at the age of 17 and 14 years old.

CONCLUSIONS:

OT-DSD is a phenotypically and genetically a heterogeneous condition. Early diagnosis and sex assignment are essential to avoid psychological and social problems. Laparoscopy has an important role in surgical diagnosis and management of such cases. Scrotal gonads should be always explored. OT is preferably to be excised.

GONADAL PATHOLOGY IN 45,X/46,XY FEMALES

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Turner syndrome (TS) and related sex chromosome abnormalities are associated with a variety of karyotypes and phenotypes affecting 1 in 2500 live births. Mosaicism with Y material (45,X/46,XY) and female phenotype is rare (<1 in 15 000 births)¹. Their risk of gonadal malignancy is 10-15%, and up to 50% in those with ambiguous phenotype at birth². We therefore examined gonadal malignancy rates in 45,X/46,XY females.

We identified 15 females aged ≤ 30 years, with 13 having 45,X/46,XY karyotype with TS phenotype, and two having non-mosaic 46,XY karyotypes with cytogenetic abnormalities consistent with TS. Of these 15 females, gonadal tissue histology was available for 14.

All 45,X/46,XY patients had a female phenotype and six had clitoromegaly at birth. Two were identified prenatally; age at diagnosis ranged from birth to 13 years, with the most common presenting features being short stature (n=6), ambiguous genitalia (n=6) and dysmorphic features (n=2). Of the 14 that underwent gonadectomy (ie 28 gonads), 9 of 16 gonads (56.3%) resected from non-virilised girls demonstrated gonadoblastoma, including three dysgerminoma in situ, with 4 arising from streak gonads, 4 from dysgenetic gonads and 1 from an ovotestis. None of the 12 gonads resected from virilised females demonstrated gonadoblastoma.

The rate of germ cell tumours in non-virilised 45,X/46,XY females (56%) is significantly higher than previously reported and the risk in virilised females (0%) is lower than previously reported², suggesting a poor correlation of risk with phenotype and the need for early gonadectomy in this group of girls.

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Prediction of germ cell cancer occurrence in postpubertal individuals with androgen insensitivity

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Background: Following reassuring data regarding the prevalence of germ cell cancer (GCC) in children with complete and partial androgen insensitivity syndrome (CAIS, PAIS), gonadectomy is now generally postponed until early adulthood in CAIS and close surveillance of gonads *in situ* proposed in males with PAIS. Although requested by many CAIS women, delaying gonadectomy further is controversial given the lack of data regarding GCC development in adulthood and the absence of reliable biomarkers for early GCC detection.

Methods: To study the prevalence of invasive GCC, carcinoma *in situ* (CIS), or signs of premalignancy (aberrant OCT3/4 and KITLG expression) at a (post)pubertal age, we performed detailed immunohistochemical studies in 94 gonadal samples (73 gonadectomy and five biopsy samples of 41 women with CAIS; nine gonadectomy and seven biopsy samples of six men and four women with PAIS). The presence of an AR mutation was genetically confirmed in all cases. All surgical procedures were performed at or after the age of 14 years (median 17 years, range 14-54 years).

Results: No invasive GCC were encountered. Premalignant changes (combined aberrant OCT3/4 and KITLG expression) were found in 8/78 (10.3%) of CAIS samples from five different women (5/41; 12.2%) at a mean age of 16.6 years (range 14-21 years); three women had bilateral changes. No signs of (pre)malignancy were found in the samples of the six PAIS men, whereas CIS was detected in one girl with PAIS (1/10; 10%) in whom gonadectomy had been performed at age 15 years.

Conclusions: The prevalence of premalignant lesions in adults with CAIS in this cohort was 12%. These lesions are already present during adolescence and are often bilateral. No prospective data exist regarding progression of such lesions to GCC. Preliminary data on a small sample point to a comparable prevalence in PAIS, with possibly a higher risk of malignant degeneration given the residual AR activity. We are currently investigating whether individuals with (pre)malignant lesions have a genetic predisposition to GCC development.

Gonadectomy Outcomes in Patients with 46,XY DSD

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BACKGROUND: Gonadectomy is indicated for those patients with disorders of sex development (DSD) and Y chromosome material considered a risk factor for malignant transformation. Gonadectomy is generally recommended for conditions known to carry a high risk of malignant transformation, but for several others, the risk is lower or unknown. This study was undertaken to assess the risk of malignant transformation of gonads in patients with 46,XY DSD.

METHODS: A retrospective chart review was performed identifying patients with 46,XY DSD who underwent gonadectomy between 1998 – 2014. De-identified demographic, genetic, clinical, laboratory, imaging, and histopathological data were collected.

RESULTS: Forty-nine patients with DSD underwent gonadectomy in 51 surgical procedures. Average age at first surgery was 8 (range 0-19) with a bimodal distribution before age 5 (49%) and after age 10 (43%). Most were reared as female (80%).

Table 1: Pathology findings after gonadectomy by diagnosis

Diagnosis	Total N (%)	Pre- Malignant* N (%)	Malignant N (%)
Complete Gonadal Dysgenesis (GCD)	11(22%)	2 (18%)	3 (27%)
Partial Gonadal Dysgenesis(PCD)	5 (10%)	4 (80%)	0
Complete Androgen Insensitivity Syndrome(CAIS)	7 (14%)	1 (14%)	0
Mosaic Turner/Mixed Gonadal Dysgenesis	13 (27%)	5 (47%)	0
17β-Hydroxysteroid Dehydrogenase Deficiency	2 (4%)	0	0
5α-Reductase Deficiency	4 (8%)	0	0
Denys-Drash Syndrome	1 (2%)	0	0
46,XY DSD, unknown diagnosis	6 (12%)	2 (40%)	0

* Pre-malignant lesions include gonadoblastoma and intratubular germ cell neoplasia (ITGCN)

Three dysgerminomas were diagnosed: two patients presented with pelvic masses at age 11 and 16, prior to CGD diagnosis. The third patient presented with primary amenorrhea at age 16, and malignancy was diagnosed at the time of her prophylactic gonadectomy for her CGD diagnosis. On pre-operative imaging, she had one gonad described as a “normal ovary.” One out of 7 patients with CAIS had a premalignant ITCGN lesion.

CONCLUSIONS: Malignancy rate was highest in those patients diagnosed with CGD (27%), and pre-malignant lesions were common in all forms of gonadal dysgenesis. Pre malignancy rate in CAIS was higher than expected in this small cohort, where many series have only observed a minimal risk.

Opening Guest Lecture

The ethics of medical care for children with DSD

Claudia Wiesemann, University of Gottingen

The medical care for children with DSD has undergone a significant change in values. Whereas in former times benevolent medical paternalism was the rule, today, the patient's right to respect for dignity and self-determination is given priority. However, the best way of safeguarding the rights of the child is still subject of considerable debate. I will discuss ethical considerations shaping the modern therapeutic management of intersex conditions that do not entail acute health risks. I will conclude with basic ethical guidelines for clinical practice.

Plenary: The Biology of Sex Development

25 years of SRY: Understanding its role in testis determination

Peter Koopman, The University of Queensland

In mammals, *Sry* (sex-determining region Y gene) is the master regulator of male sex determination. However, its regulation and function at the molecular and cellular levels have been difficult to study and remain poorly understood. Largely as a consequence of its location on the Y chromosome, its ability to drive the complex pathway of testis development is fragile, a situation that has profound biological, medical and evolutionary implications.

The transcription factor encoded by *Sry* comprises a conserved high-mobility group (HMG) box DNA binding domain and poorly conserved regions outside the HMG box. To dissect the molecular functions of mouse *Sry*, we generated a series of mutants, and studied their biochemical properties in cell lines and transgenic mouse embryos. Our findings indicate that mouse *Sry* has evolved a novel bifunctional module, whereas SRY proteins in other taxa including humans seem to lack this module, presumably making them dependent on partner protein(s) for their ability to activate target gene transcription.

Sry activates expression of a related *Sox* gene, *Sox9*, that then activates a suite of genes required for maintaining the Sertoli cell phenotype and directing the development of other testicular cell lineages. Once *Sox9* is activated, several pathways are activated that ensure continued expression of *Sox9* and recruitment of Sertoli cell precursors that do not express sufficient levels of *Sry* to cell-autonomously upregulate *Sox9*.

Our studies of a mouse model of ovotestis development indicated that both timing and levels of SRY expression are critical for SOX9 expression. Therefore, regulatory mutations affecting *Sry* expression levels or timing may therefore explain some idiopathic XY DSD cases.

We have used a number of approaches aimed at identifying mouse *Sry* 5' flanking sequences that may be critical for *Sry* regulation. The recent development of genome editing technologies such as the CRISPR/Cas-9 system offers a rapid, efficient, versatile and precise means of locating and functionally analysing such sequences. I will present our recent progress in understanding *Sry* regulation using CRISPR/Cas-9 experiments in mice.

DMRT1 AND GONADAL CELL FATE REGULATION, FROM GENOMIC TO ATOMIC SCALE

David Zarkower, University of Minnesota

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DMRT transcription factors regulate sexual differentiation in most multicellular animals. DMRT1 regulates sex determination in some vertebrates and testicular differentiation in others. In the mouse DMRT1 also regulates fetal germ cell development, controls the mitosis/meiosis switch in male germ cells and is required to prevent transdifferentiation of testicular Sertoli cells to their female equivalent, granulosa cells. We have addressed how and why DMRT1 regulates male fates in somatic cells of the testis using methods ranging from genetics and genomics to structural biology.

When DMRT1 is missing, Sertoli cells sexually transdifferentiate, starting in the first postnatal week. Mutant cells ectopically express many genes normally involved in ovarian sex determination and differentiation, including *Foxl2*, estrogen receptors, and Wnt pathway components. We used genetic analysis to show that these genes are required to drive sexual transdifferentiation in *Dmrt1* mutants. We also showed that DMRT1 overexpression in the ovary can cause sexual transdifferentiation of granulosa cells. We next asked what feminizing mechanism DMRT1 inhibits to maintain male fate. Retinoic acid (RA) is a prime candidate, given its central role in spermatogenesis starting shortly after birth. Indeed, increasing RA enhances transdifferentiation and inhibiting RA synthesis or deleting the receptor *Rara* suppresses it. Our results indicate that DMRT1 allows Sertoli cells to participate in RA signaling, which is essential for reproduction, without being reprogrammed to a female fate.

DMRT proteins share a conserved novel DNA binding domain and bind a conserved DNA sequence, but how they recognize target genes to control sexual differentiation has been unknown. We combined X-ray crystallography with in vitro and in vivo molecular analyses including ChIP-exo to show that DMRT1 is surprisingly versatile in how it interacts with DNA and can bind as a dimer, trimer or tetramer. Binding involves insertion of two recognition helices into the same DNA major groove, a mode of protein/DNA interaction not observed

previously. Molecular modeling indicates that Doublesex in flies and MAB-3 in nematodes also bind DNA using distinct modes. Finally, we found that point mutations affecting conserved amino acid residues critical for sequence-specific DNA recognition are associated with sex-reversal in both flies and humans. Our results illuminate in atomic detail a molecular interaction that has controlled metazoan sexual development and likely shaped evolution for hundreds of millions of years.

Molecular mechanisms of Androgen actions for external genitalia formation

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Sexually dimorphic development of embryos is achieved by organ differentiation. Our body is composed with organs showing numerous sexual differences and dimorphism. Such mechanisms of sexual differences can be typically observed in reproductive organ formation. Among them, the mechanism of masculinization is one of the central topics in developmental biology. Although it was shown that androgen establishes the male sexual characteristics, the involvement of locally produced "effectors" remains unknown. Such coordinated actions of androgen and the effector genes were genetically analyzed on mammalian external genitalia formation with series of mutant mouse models. We have been analyzing on the role of several developmental regulators for mouse external genitalia formation (Since our first work by Haraguchi et. al. Development 2000, 2001).

Recently we identified transcriptional factor MafB for the development of mouse external genitalia. MafB expression is induced immediately by androgen exposure and it is indispensable for male type urethra formation. Its unique-mode of gene regulation and recent advancement will be discussed.

Parallel Session: Processes, Not Events: Achieving Better Long-term Outcomes

The *event* of diagnosis is only the start of a journey. Children and their families need to be cared for in *a process* of joined-up support and interventions that might last 2 decades and more.

This parallel session, hosted by the Dutch support group DSDNederland and the on-line resource www.dsdfamilies.org, aims to explore a number of processes that bring about successful long term outcomes, such as health, mental wellbeing, sexual pleasure and social integration.

From I-DSD Glasgow to I-DSD Ghent: from 'patient groups' to 'partners'?

Ellie Magritte, Joke Gorter-Bouma, dsdfamilies, dsdnederland

Working Together in Raising Confident Young Men

Tiger Devore, Hypospadias/Epispedias Association

Precious little information exists about how to discuss early sexual exploration with young men with 46, XY DSD. This presentation offers a positive long-term communication model for fathers –in collaboration with the team- to talk to sons in a way that promotes self-esteem and confidence and reduces the anxiety of young men when sharing information with a potential sexual partner about their DSD

Informed consent: from ethical principles to ethical behaviour

Lih-Mei Liao, University College London Hospitals

Informed consent has been described as communication between provider and recipient, whereby the recipient understands equally the immediate and longer term implications of the proposed intervention as well as the alternatives, including no intervention. This process may be compromised by a number of psychological factors. This paper outlines a behavioural checklist developed at UCLH to optimise quality and consistency in the consenting process for adult women electing to undergo (further) genital surgery.

Building partnerships to enhance health literacy and facilitate peer-to-peer support

Various invited speakers

To kick-start this discussion we will invite a range of short contributions on information needs from different families and on initiatives that have improved health literacy and/or provide peer-to-peer support, including the introduction of a new on-line resource www.dsuteens.org .

Parallel Session: Clinical Psychology: Stress and Distress in DSD

Posttraumatic Stress in Parents of Children Diagnosed with DSD: Research Findings and Clinical Implications

V Pasterski, University of Cambridge

Though clinical impression has long indicated that parents of children diagnosed with DSD are particularly vulnerable to increased levels of distress, a clear picture of which diagnostic conditions or clinical features have the greatest impact on parental well-being is only just emerging. Factors which have historically been considered as potential stressors include genital ambiguity, corrective urogenital surgical intervention, sex assignment /reassignment, (lack of) provision of psychological support and communication patterns between health care providers and parents.

The Consensus Statement for clinical management of DSD issued guidelines for clinical management addressing these factors and highlighted the particular need for psychological support for parents/patients/families with the aim of alleviating distress subsequent to unique challenges inherent in DSD. However, efficacy of such service provision has been limited by several critical factors: (1) lack of understanding of the precise nature of parental distress; (2) lack of understanding of conditions and features predictive of distress; and (3) lack of uptake of even the most basic added support provided by psychological services.

Primary aims of the current report were to identify the nature and intensity of parental distress and to elucidate patient/family characteristics and diagnostic conditions predictive of distress. In-depth interviews were conducted with 47 parents (36 mothers and 11 fathers, representing 33 families) and measures of mental health functioning, including levels of posttraumatic stress symptoms (PTSS), were obtained. Analyses identified posttraumatic stress to be of particular clinical relevance. Thirty-one percent of mothers and 18% of fathers met the clinical threshold for Posttraumatic Stress Disorder (PTSD); and intensity of PTSS were similar to those reported for parents of children diagnosed with cancer. Furthermore, regression analysis revealed that confusion about the DSD diagnosis/prognosis accounted for the most variance in PTSS. Factors which were not predictive of PTSS were genital ambiguity, sex of rearing, sex of parent and emotional response (i.e., shock, anger, guilt, grief). These findings support previous reports suggesting that uncertainty about diagnosis/prognosis may be considered as a target for clinical intervention. Relationships between other mental health factors and societal perceptions of validity and remit of psychological support services will also be discussed.

Parental narratives about their child's genital ambiguity – protection and decisions on genital surgery

C Sanders, Alder Hey Hospital

The maternal instinct and mother baby bond could be challenged following the birth of a baby with DSD. Parents have been reported as experiencing a range of emotions and psychological stressors which include; sorrow, shock, anger, situational stigma and post-traumatic stress. Any of these experiences can contribute to an increased psychosocial burden for parents of a child with DSD.

Parenting has a role and responsibility within many cultures and generally involves protecting their child from physical and psychological harm. Within this there are often strong protective emotional responses founded on parents own experiences, social, cultural and spiritual norms and wider social influences. Considering a model of protection motivational theory (PMT) may help us to explore where the role of genital surgery may fit within parents thinking and how in turn this could influence their decision making.

EMOTIONAL DISTRESS IN INDONESIANS WITH A DISORDER OF SEX DEVELOPMENT

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Introduction

In order to optimize psychosocial well-being and social participation, clinical management of DSD includes gender assignment and medical interventions to prevent or correct physical ambiguity. This policy has been criticized for imposing male/female gender and genital surgery in young children. It has been argued that such interventions reflect non-acceptance of DSD and obstruct psychosocial well-being. Despite the critique, most parents choose gender assignment and prevention/correction of physical ambiguity, making it difficult to study potential adverse influences of physical ambiguity on psychosocial well-being.

In Indonesia, diagnostic evaluation and treatment facilities for DSD recently became available. Many individuals with DSD lived with an ambiguous physical appearance and grew up in doubts about their gender. We studied patients and parents' experiences of being raised in ambiguity and its consequences on emotional distress and social stigmatization.

Methods

Design: Comparison between individuals with DSD and healthy control subjects matched for gender, age and socioeconomic status.

Individuals with DSD: 60 children, 24 adolescents and 34 adults. Ages 6 – 41.

Measures: Social stigmatization (SSS-DSD); emotional functioning (CBCL,YSR, ASR) and quality of life (TACQOL/TAAQOL).

Results

Social stigmatization was experienced by individuals with a. visible physical ambiguity (children $p=.002$; adults $p=.001$) b. who displayed cross gender behavior ($p<.001$) and by c. individuals who changed gender (children $p=.02$; adults $p=.03$). Rejection elicited depression and isolation (children $p=.002$; adults $p=.009$). Children suffered more social problems ($p=.03$) and adults reported more anxiety and depression ($p=.02$) than controls. On quality of life parents reported hampered social functioning ($p<.001$) and decreased happiness in girls ($p=.003$); adult patients reported more depression ($p=.05$) and women more anger ($p=.02$) than controls.

Conclusion

Many Indonesian individuals with DSD experienced social stigmatization and other barriers in social functioning. Stigmatization and hampered social functioning was related to emotional distress. These findings support the assumption that visible physical ambiguity is adverse for social participation and quality of life.

Education on DSD and medical interventions to prevent visible physical ambiguity may remove barriers for acceptance. Referral to multidisciplinary teams immediately after

identification of DSD is recommended. Psychological interventions such as counseling, coping strategies and empowerment should be integrated into the treatment plan.

Multidisciplinary approach in vaginal dilation therapy

B. Van Hoorde - B. Stockman, University of Ghent

Research has shown that vaginal dilation treatment is a (cost) effective first line alternative to vaginal surgery. It also has a less invasive character and fewer complications. However, it may have a negative emotional impact on the women. It is also a time consuming exercise and success seems to be directly related to compliance.

We start with an appointment performed by a gynaecologist which include a vaginal examination. It is followed by at least one therapy session by a clinical psychologist. The purpose of this session is to identify any contraindications to using dilators and the evaluation of the maturity and the motivation of the patient.

The psychologist does a general survey and also a more relational and sexual one. In the session we provide information about their condition en we teach some sex education. We evaluate whether the patient is ready for this vaginal dilation treatment. If so, then we can refer to the physiotherapist.

If it is necessary or desired, the clinical psychologist follows the patient during the whole process.

The role of the physiotherapist in vaginal dilation in woman with DSD is divided in two parts, on the one hand the fact of giving full information about the functioning and sensation of the pelvic floor area and genital zone, and on the other hand the guidance on the effective dilation. The knowledge of the functioning of the body and the entire dilation technique will build confidence in the therapy ,therapist and the forecast of the dilation.

The physiotherapist has a few techniques to familiarize the patient with the own pelvic area and the functioning of this during the dilation. The personal guidance in placing the vaginal probes will be one of the most important tasks of the therapist.

The evaluation of the situation and the measurements of the depth of the dimple after a period of 6 weeks will be a motivation for the patient and will focuses the medical team already in their prognosis.

Long Oral Communications

Massively parallel sequencing of a targeted panel for the diagnosis of DSD.

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Disorders of Sex Development (DSDs) are congenital conditions in which development of gonadal or anatomical sex is atypical. The cause is most often a breakdown of the complex network of gene regulation responsible for proper development of testes or ovaries. Currently, most DSD patients cannot be given an accurate diagnosis, which severely comprises their clinical management. We aim to identify the underlying changes in genes associated with DSD in an effort to provide an accurate diagnosis as well as gaining insights into gonad development. As part of this study we have assembled a large cohort of DSD patient samples (1,053 DSD patient DNA samples, comprising 60% 46,XY DSD, 5% 46,XX DSD, 15% unexplained androgen insensitivity; 3% premature ovarian failure; 17% DSD with other syndromes).

We have developed a targeted DSD panel combined with massively parallel sequencing for the in depth analysis of up to 1,034 genes. This DSD gene panel includes all known high frequency genes (eg *SRY*, *SOX9*, *NR5A1*), low frequency genes (eg *CBX2*) and entire gene pathways (eg Androgen, *WNT*, *MAPK*, *TGF β* pathways). In addition, the panel includes potential novel DSD genes, small regulatory regions and miRNAs. The DSD targeted panel is relatively inexpensive, has excellent coverage (relative to exomes) and is quick to analyse allowing rapid turn-around in a clinical diagnostic setting.

In a pilot study of 300 patients we were able to provide a diagnosis for 40% of DSD patients. This is a substantial increase in diagnostic rates compared to all other methodologies. In addition, the panel allows us to detect the sex chromosome complement as well as large and small deletions and duplications (CNVs) affecting known DSD genes. The targeted DSD panel is undergoing clinical accreditation for implementation by the Victorian Clinical Genetics Service as a certified clinical diagnostic test. We believe that rapid, accurate diagnosis of DSD patients will assist in their clinical management and improve patient outcomes.

A new Next Generation Sequencing panel for mutational screening of putative genes causing 46, XY Disorders of Sex Development (DSD).

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Disorders (or Differences) of Sex Development (DSD) are rare congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. Currently the genetic causes in about 50% of 46,XY cases are unknown. Thus we have developed a customized AmpliSeq 46,XY next generation sequencing (NGS) gene panel that allows a rapid and cost-effective screening of mutations in 46,XY DSD.

Our “DSD gene panel” includes 83 genes, that are already described to be mutated in patients with 46,XY DSD or were selected as interesting candidate genes based on functional investigations in human or animal model systems. In addition to the coding regions of the genes the splice-sites were included. Using the AmpliSeq Designer Tool the gene panel was designed in two libraries of approx. 600 amplicons each, covering ~96,5% of target regions. These amplicons were sequenced by an ION Torrent PGM (personal genome maschine). The sequences were aligned to a reference sequence and the Variant Caller Files were annotated with ExAC Browser, dbSNP, 1000genomes or the Exome Sequencing Project 6500. The pathogenicity was determined using different mutation prediction tools like SIFT, PolyPhen 2 or the MutationTaster. The coverage and validity of mutations were reviewed with Bam-Files in the Integrative Genome Viewer.

So far we have sequenced 32 samples within six panel experiments. Four of these patients with known causative mutations were included as controls and all their mutations were identified. The remaining 28 samples came from patients with unknown cause for 46,XY DSD. For five patients we found likely pathogenic mutations in *HSD17B3*, *CHD7*, *WWOX*, *DHH*, *MAMLD1* and *DGKK*. All of these mutations were confirmed by Sanger-Sequencing.

We conclude that NGS panel sequencing allows a targeted mutational screening of many genes simultaneously in a short time with a high sensitivity, less cost and a small amount of DNA. This will benefit research investigations for better description of unusual phenotypes in 46,XY DSD and might be embedded into future diagnostics of these patients.

Identification and functional characterization of ESR2, a new disease gene for 46,XY disorders of sex development (DSD).

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Background: Today the molecular cause of a disorder of sex development (DSD) is established in only 20-40% of cases. The advent of newer genetic technologies such as next generation sequencing applications like exome sequencing, will enhance the identification of new genes involved in DSD. Here, we used homozygosity mapping in a Turkish patient with syndromic 46,XY DSD and a consanguineous background to identify the causal gene defect.

Results: We identified a potential functional candidate gene for DSD in the largest homozygous region (chr 14) namely *ESR2*, encoding the Estrogen Receptor beta. Sanger sequencing revealed a homozygous in-frame deletion in *ESR2* in this patient, c.541_543del (p.Asn181del). Segregation analysis showed that both parents and a healthy sibling are heterozygous carriers for the mutation; another healthy sibling is homozygous for the wild type allele. The deleted amino acid is located in the functionally important DNA-binding domain and is highly conserved (up to Tetraodon). This deletion was absent in an ethnically matched control population. *ESR2* mutation screening in a 46,XY DSD cohort revealed an additional heterozygous mutation c.251G>T (p.Gly84Val). Different prediction programs suggest an alteration of protein function (SIFT, Polyphen, Mutation Taster). In addition the affected amino acid is conserved up to fruitfly.

To exclude the presence of other possibly damaging variants, we performed exome sequencing. After extensive filtering and confirmation of the data, we could not identify other potentially interesting variants.

Immunohistochemistry in an 8-weeks old human male embryo showed ER-beta expression in the hindgut and the eyes, which might recapitulate the systemic manifestations of the index case.

Dose-response assays with DPN, different luciferase constructs, and ER-beta wild type and mutant constructs in HEK293T cells showed a differential transcriptional activation of the ER-beta mutants.

Expression analysis of different ER-beta targetgenes remained inconclusive. Localization studies did not show an aberrant subcellular expression pattern for the mutated *ESR2*.

Conclusions: Our study sustains a role of *ESR2* as novel disease gene for syndromic 46,XY DSD. Additional functional studies will provide insights into their molecular consequences and into the role of *ESR2* in the pathogenesis of 46,XY DSD. At the moment our experiments

are only focussed on the classical way of ER signalling, exploration of other ER pathways might also shed a light on the involved mechanisms.

Hormonal evaluation in relation to phenotype and genotype in 286 patients with a Disorder of Sex Development (DSD) from Indonesia

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Background

DSD cover many different phenotypes of atypical sexual anatomy. The etiological spectrum is broad. Many genes are involved in known pathways that lead to gonadal formation and differentiation. In addition, potentially novel and alternative pathways may play a role

Results

286 patients with atypical external and/or internal genitalia from Semarang, Indonesia, previously undiagnosed and referred between 2004 and 2010 were included. The diagnostic evaluation included clinical, imaging, hormonal, molecular genetics, and histological parameters.

The age at presentation was 0-0.5 years in 14.3% cases, >0.5-12 years in 63.3% cases, and >12 years in 22.4% cases. The karyotypes of patients as follow : 46,XY DSD 68.2%, 46,XX DSD 23.4% ,sex chromosomal DSD. In 61.2 % of the 46,XX DSD patients,17.9% of the 46,XY DSD patients and all sex chromosome DSD patients (29.4% in total) a final diagnosis was reached based on genetic or histological evaluation. Serum concentrations of 17-hydroxyprogesterone and androstenedione were the most distinctive parameters in 46,XX DSD patients in whom Congenital Adrenal Hyperplasia was the most common diagnosis (59.7%). In the remaining 40.3% patients categorized 46,XX DSD, the concentrations of LH, FSH, T and AMH were the subsequent parameters to establish gonadal function. In 46,XY DSD the following diagnostic groups were identified based on the external masculinization score: androgen action disorder (AAD), unknown male under masculinization (UMU). Serum values of LH, FSH and basal testosterone differed between AAD and UMU versus Gonadal

Dysgenesis (GD), particularly in post pubertal patients. HCG tests were of no additional value as no patients with androgen synthesis disorders were found. Gene mutations were found in all patients with CAH, but in only 24.5% and 1.8 % patients with AAD and UMU respectively. In 32% of 46,XY GD patients copy number variants of several genes were found.

Conclusion

A stepwise practical diagnostic approach in a large cohort of DSD patients in Indonesia led to a molecularly or histologically proven final diagnosis in 29.4 % of the patients. Most helpful parameters were serum levels of 17-hydroxyprogesterone and androstenedione in 46,XX DSD patients and of LH, FSH and basal testosterone in 46,XY DSD

Diagnostic Approach To A Newborn With Suspected DSD - Results From An International Survey Of Specialist Care For DSD.

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Background: The approach to investigating a newborn with a suspected DSD is likely to vary between centres and may be influenced by local availability and technological developments.

Methods: To explore the current diagnostic practice and needs, an international survey of 124 paediatric endocrinologists, identified through DSDnet and the I-DSD Registry, was performed in the last quarter of 2014.

Results: A total of 77/124(62%) clinicians, in 74 centres, from 38/42(91%) countries responded to the survey. In a suspected case of 46,XY DSD, the investigations that would be performed routinely within the first week of presentation included testosterone(97%), karyotype(96%), ultrasound(94%), 17-OHP(83%), androstenedione (75%), DHT (73%), X/Y probes by FISH/PCR(69%), cortisol(68%) and AMH(58%). Second-line investigations included further imaging(86%), array CGH(69%), cortisol ACTH stimulation(69%), hCG stimulation test(62%) and urinary steroid profile(USP)(51%). The diagnostic tests reported to be not available locally but desirable included USP(43%), array CGH(31%), DHT(21%) and AMH(21%). Clinicians reported that, locally, they had access to the following genetic tests: *SRY*(75%), *AR*(66%), *SRD5A2*(53%), *NR5A1*(53%), exomic/genomic analysis(51%), *WT1*(51%), *DAX1*(49%), *SOX9*(44%) and a wider panel of genes(44%). The genetic tests the clinicians would perform routinely in a case of 46,XY DSD included: *SRY*(51%), *AR*(43%), *SRD5A2*(31%) and *NR5A1*(26%), while they would perform *DAX1*(73%), *WT1*(71%), *NR5A1*(65%), *SRD5A2*(62%) and *SOX9*(61%) only if family history or biochemistry were suggestive. For diagnosing 5α reductase deficiency, 49% clinicians reported genetic testing as the single

most preferable test whilst 38% and 13% reported testosterone:DHT ratio and USP, respectively. The corresponding figures for 17 β HSD3 deficiency were 55%, 32% and 13%.

Conclusion: There is considerable variation in the diagnostic evaluation of a newborn with suspected DSD between centres and access to specialist tests may influence this factor. Molecular genetic testing is increasingly common in specialist centres. Clearer guidance in complex cases and collaboration through a network of centres could rationalise the need as well as access to diagnostic investigations for DSD.

Long-Term Endocrine Outcome In Men With Partial Androgen Insensitivity Syndrome

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Background: Partial Androgen Insensitivity Syndrome (PAIS) is a rare condition which is associated with a variable phenotype. To date, there are limited conclusive data reporting long-term endocrine outcome for this condition.

Aims: To determine the outcomes and clinical characteristics for 46,XY males with PAIS, using information from the International DSD (I-DSD) Registry and its clinical users.

Methods: The I-DSD Registry and its users were approached to identify all male participants registered as having PAIS and who were over the age of 14 years at the time of study. Each user reporting a case was contacted to obtain further clinical information. Information was collected regarding date of initial presentation with PAIS, presence/absence of an AR mutation, clinical characteristics, biochemical characteristics and treatments received since diagnosis.

Results: A total of 60 men over the age of 14 years from 9 different countries were reported as having PAIS at the time of data collection. The median age at time of data collection was 24 years (range 15-60). Of these cases, 37 (62%) had a confirmed AR receptor mutation. Of

those with a confirmed AR receptor mutation, median external masculinisation score (EMS) at first and last presentation was 7 and 9 (3-12), respectively. Median FSH levels at first and last presentation were 1.97mIU/ml (0.1-50) and 5.2mIU/ml (1.15-89), respectively. Median LH levels at first and last presentation were 4.82mIU/ml (0.04-36) and 9.3mIU/ml (1.15-89). Eighteen (49%) of these patients required testosterone therapy at some point between diagnosis and date of data collection. In terms of surgical intervention, 7(19%) had required 1 or 2 hypospadias operations whilst 7(19%) had required >2 hypospadias operations. 2 (5%) had required unilateral orchidopexy and 11(30%) had required bilateral orchidopexy and in adulthood, 4(11%) had required mastectomy. Only one person(2%) was reported to have required treatment for testicular cancer.

Conclusion: Boys with PAIS have a higher likelihood of multiple operations for hypospadias and over 50% virilise without the need for testosterone therapy. Gynaecomastia that is severe enough to require mastectomy is not an uncommon outcome. These data will aid in the long-term management of boys with PAIS with a confirmed AR mutation.

Bone mineral density in women with complete androgen insensitivity syndrome: effects of gonadal removal and sex steroids substitutive therapy

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Background. Women with complete androgen insensitivity syndrome (CAIS) may have impaired bone mineral density (BMD) due to androgen resistance and gonadal removal. It remain to be established if intact gonads may have protective effects on BMD and if hormone replacement therapy (HRT) may permit the normal BMD values in women with CAIS and removed gonads.

Aim. To assess BMD in women with CAIS and intact or removed gonads and to relate BMD with compliance with HRT.

Patients and methods. A group of late adolescents and adult women with CAIS (n = 53; age 30.4 ± 9.4 years) were investigated. Androgen receptor mutations were detected in all the subjects. Fourth-three women had removed gonads: compliance with HRT was rated as good (25/43, subgroup A) or poor (18/43, subgroup B). Ten women had intact testes (subgroup C). BMD was assessed by DXA at femoral neck (FN) and lumbar spine (L2-L4).

Results. Mean BMD values in the total group of women with CAIS were significantly reduced at each measured site (FN-BMD: -0.96 ± 1.18 SDS, p = 0.0044; L2-L4-BMD: -1.70 ± 0.92 SDS, p = 0.0000). Women of subgroup B had significantly lower BMD values at all measured sites in comparison with subgroups A and C. In addition, patients of subgroup A had lower BMD

values than women of subgroup C. In group A and B, BMD was significantly reduced at each measured site, while in group C was not.

Conclusions. In women with CAIS, lumbar BMD was more affected than FN-BMD. Women with removed gonads showed lower BMD in comparison with those with intact gonads. Compliance with HRT improved - but it did not normalize - BMD status in women with CAIS who had their gonads removed. Thus, bone health represents a main issue for women with CAIS, mainly when gonads are not *in situ*.

Brain white matter microstructure in women with CAIS

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Background

Sex hormones, androgens in particular, are believed to play a key role in the sexual differentiation of the human brain. However, possible direct effects of the sex chromosomes, i.e. XX or XY, have not been well studied in humans. Since women with Complete Androgen Insensitivity Syndrome lack androgen action in the presence of XY-chromosomes, they provide us with a unique opportunity to study the separate effects of androgens and sex chromosomal composition on the sexual differentiation of the brain.

Methods

MRI-scans of the brain were acquired from 20 women with CAIS, 30 control men and 30 control women. Diffusion tensor images (DTI) were used to calculate fractional anisotropy (FA) maps, which provide information about the white matter microstructure of the brain. First, comparisons of these FA maps were made between control men and women in order to replicate previously reported sex differences. Subsequently, the FA maps of women with CAIS were compared to both control groups.

Results

Previously reported sex differences in FA were replicated, with higher FA values in men than in women in multiple white matter regions. Men also showed higher FA values than women with CAIS in several white matter tracts, and many of these regions showed an overlap with the difference between the control groups. No differences were found between control women and women with CAIS.

Conclusions

Fractional anisotropy of the white matter is female-typical in women with CAIS. These results provide evidence that sex differences in white matter microstructure are most likely

not directly driven by sex chromosomal composition, but rather reflect gonadal hormone exposure.

Neoplastic risk of dysgenetic testes

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Background

Dysgenetic gonads in patients with Y chromosome are usually resected in childhood because of the high risk of germ cell tumours (GCT). However, the real risk is unknown because of relatively low number of adult patients with preserved dysgenetic gonads. The aim of the study was to evaluate the prevalence of neoplastic lesions in dysgenetic gonads in children and adults.

Materials and methods

We evaluated 94 patients with gonadal dysgenesis (GD), aged 1.2-32 years (47 prepubertal, 1.2-10 years; 47 pubertal/adult, 13-32 years), with Y chromosome in the karyotype. Serum levels of FSH, LH and testosterone were determined. Bilateral gonadectomy was performed in 73.4% of patients, while in 26.4% - unilateral with biopsy of the contralateral gonad. Gonadal tissues were histologically evaluated, including immunohistochemical reaction with antibodies against PLAP and Oct-3/4 (markers of malignant germ cells) in all, as well as c-Kit in prepubertal patients.

Results

Streak gonads on both sides (complete GD) were recognised in 30.8% of cases, a streak gonad on one side and an underdeveloped testis on the other (asymmetric GD) in 38.3% and underdeveloped testicular structure on both sides (partial GD) in 30.8%. Germ cell neoplastic lesions were found in 53.2% of patients (51.1% in children, 55.3% in pubertal/adults). Invasive GCT were revealed in 11.7% of cases, among them 90.9% in pubertal/adult patients. Other neoplastic lesions included gonadoblastoma and testicular *carcinoma in situ* with the prevalence 16% and 25.5%, respectively. Hypergonadotropic hypogonadism was diagnosed in most of the pubertal/adult patients (mean: FSH - 54.2±23.3 IU/L, LH - 21.7±12.1 IU/L, testosterone - 5.5±4.5 nmol/L).

Conclusions

Dysgenetic gonads in patients with Y chromosome have a high risk of germ cell neoplasia (ca. 50%). If they are preserved until puberty/early adulthood they may develop overt, invasive GCT. The gonads have also poor hormonal activity (hypergonadotropic

hypogonadism) in most of the patients. If dysgenetic gonads are not resected in childhood, these patients need careful and constant follow-up.

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Plenary: The Complexities of Phenotypic Assessment

Comprehensive clinical phenotyping of DSD

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Standardized phenotyping is of fundamental importance in management of Differences or Disorders of Sex Development (DSD). Classification and assessment of the phenotype is difficult, time consuming, prone to observer bias and inter-observer difference, changing over time and social-cultural background, and there is no consensus on how to assess. According to the Chicago consensus from 2006 clinical evaluation includes history, physical examination with assessment of the genital anatomy in comparison with the norm (from nomograms) and recording of the findings. Thorough clinical examination is the prerequisite of assessment and is fundamental for gender assignment and usually there is significant association between sex of rearing and external genital appearance. Standardized assessment should be used as a means of objectively documenting the degree of masculinization in cases of male under- and female overmasculinization, respectively. All forms of assessment should follow a standardized approach. This includes measurement, documentation, photography, nomenclature, definitions and scoring. Standardized documentation and prospective recording of data will facilitate quality control and audit and will enhance comparability. Intra- and interobserver bias and error should be minimized. The goal is to keep assessment easy to perform, non-time-consuming, with a maximum of reliability, objectivity, and reliablitiy. Moreover, prospective collection of standardized assessment provides a means of connecting clinical and research centers around the world within a virtual environment and allows these experts to enter standardized information that will improve clinical practice, research and understanding of these challenging conditions. In this talk the historical background, important items of assessment, current tools (Prader classification, external masculinization score and internal masculinization score, Rink classification, HOPE score) and a proposal of how to assess in a standardized way in the future within the I-DSD database is discussed.

Sex steroid synthesis (SSS)

Christa E. Flück, University of Bern, Switzerland

Physiology of SSS - Sex steroids are predominantly produced in the gonads. But during fetal life the adrenals and the fetal-placental unit play an important role for androgen metabolism. In addition, steroid enzymes in peripheral tissues may influence the sex steroid profile. The biochemistry of classic sex steroid (both testosterone and estrogen) synthesis from cholesterol in the testis and the ovary is well known. However, in recent years an

alternative pathway which can produce the very potent dihydrotestosterone from 17-hydroxyprogesterone without going through testosterone has been discovered from studies of tammar wallaby pouch youngs. Although we found human mutations in enzymes (AKR1C2/4) involved in this “backdoor” pathway in patients with 46,XY DSD, the role of this novel pathway remains largely unsolved.

Disorders of SSS causing 46,XY and/or 46,XX DSD – Human mutations are known for almost all genes encoding enzymes or cofactors involved in SSS. Defects in genes responsible for SSS only cause isolated SSS disorders (46,XY DSD: CYB5A, HSD17B3, SRD5A2, AKR1C2/4; 46,XX DSD: CYP19A1). By contrast, defects in genes which are also involved in mineralocorticoid and glucocorticoid biosynthesis cause the various forms of congenital adrenal hyperplasia that are associated with adrenal insufficiency and SS deficiency or excess (StAR, CYP11A1, HSD3B2, CYP17A1, CYP21A2, CYP11B1 and POR).

How to assess SSS – Measurements of steroids are possible from blood, urine and other specimens. For practical reasons, routine measurements have been performed mostly with immunoassays. However, especially for SS, these assays are quite inaccurate. Therefore, it is now recommended to assess steroids with chromatographic-mass spectrometric methods. These methods are highly specific and permit the measurement of a full steroid profile which facilitates the diagnosis of complex steroid disorders. However, diagnostic confirmation of inherited steroid disorders requires a genetic analysis.

Neural correlates of steroid disorders

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Not much is known about the influence of early changes in the hormonal milieu, and sex steroid hormones such as androgens in particular, on the neurobiological basis of socio-affective processing. Knowledge on underlying neurobiology may be important, however, as some affected individuals suffer from a higher rate of affective disorders pointing at possible links between hormones and mental well-being. In this talk, I will present data from three lines of magnetic resonance imaging (MRI) studies in adolescents suffering from Congenital Adrenal Hyperplasia (CAH) and Familial Male Precocious Puberty (FMPP, testotoxicosis) and adults with Complete Androgen Insensitivity Syndrome (CAIS). Adolescents with CAH and FMPP performed emotional and emotional memory tasks while undergoing MRI scanning. The data indicated changes in neural activation, relative to unaffected controls, in the amygdala and hippocampus during fear processing. Adults with CAIS completed a sexual arousal task and a task mirroring social rejection (the cyberball paradigm) to examine positive and negative feelings. The advantages and disadvantages for comparing across steroid disorders will be considered and the results will be integrated with recent models that suggest links between anxiety and depression and changes in sex steroid levels. Finally, some potential implications for therapy and management of affected individuals will be discussed.

Plenary: The Gonad and its Long-term Outcome

Endocrine disruptors and their effects on gonadal function

Olle Söder, Karolinska Institute

Approximately 1:4,000 children are born with atypical appearance of their genitalia as part of a more or less defined disorder of sex development (DSD). Due to improved medical knowledge and better classification, the etiology and pathophysiology behind a growing number of these cases have been clarified, and there are growing insights into the functional consequences for sex differentiation of chromosomal aberrations and defined genetic defects. However a large number of cases of DSD still remain obscure with respect to the underlying background and seem to be associated with environmental rather than genetic causes. Data to support this comes from recently observed declines in human male fertility in parallel with observations of poorer semen quality in young adult males. Congenital abnormalities in boys such as cryptorchidism and hypospadias also appear to be increasing. Reported regional variations of such observations strengthen the possible association with environmental factors. Endocrine disrupting chemicals (EDCs) is the term used for an expanding number of exogenous chemicals with the ability to influence the endocrine system. EDCs have been firmly associated with observations made world-wide on reproductive malformations and dysfunctions in numerous species of wild-life and there is emerging evidence of similar associations also in humans. In experimental models EDCs have been found to disrupt gonadal maturation and function. Gender dimorphic actions have been observed although most studies point to a particular vulnerability of the testis. Androgen production by Leydig cells and action on target cells are critical for normal male pre and postnatal testicular development and constitute a potential target for EDC action. This presentation will give an overview of the concept of environmental disruption of gonadal function with focus on the possible role of some defined EDCs.

GCC risk profiles: relevance for DSD.

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Development of malignant germ cell tumors, also referred to as Germ Cell Cancer (GCC), is a well-known risk factor for certain variants of DSD (Disorders of Sex Development/Differences of Sex Development). However, so far, the actual risk is hard to predict for every individual with a high level of confidence. This hampers the decision making for possible (prophylactic) treatment in individual(high risk) cases. GCC originate from a Primordial Germ Cell (PGC)/gonocyte, blocked in its process of maturation. This is highly dependent on their micro-environment, determined by formation of the gonadal supportive cells, i.p. Sertoli and Granulose cells, in a male (XY) or female (XX) context, respectively. The precursor lesion is classified as Carcinoma *In Situ* (CIS)/Intratubular Germ Cell Neoplasia Unclassified (IGCNU) within a testis, and Gonadoblastoma (GB) in an ovary or dysgenetic gonad. CIS/IGCNU will be reclassified as Germ Cell Neoplasia *In Situ* (GCNIS) in the upcoming WHO classification system (2016). The precursor germ cells of GCC are

characterized by a nuclear presence of the pluripotency marker OCT3/4 (POU5F1). In addition, individuals with DSD are at a higher risk for GCC development if part of the Y chromosome, known as GonadoBlastoma on the Y chromosome (GBY) is present in the karyotype, for which TSPY is the expected candidate, expressed in the precursor lesions. KITLG is found to distinguish embryonic germ cells delayed in their physiological process of maturation from the premalignant germ cells (i.e., the latter being positive). These parameters are all determined based on histological evaluation of gonadal tissue. Genome Wide Association studies (GWAS) on GCC of adult males indicated a series of Single Nucleotide Polymorphisms (SNPs) associated with this cancer. Interestingly, these map to a limited number of highly relevant pathways, including gonadal development (DMRT1), embryonic germ cell proliferation and maintenance (KITLG, SPRY4, TERT, BAK1, etc). A unifying model will be presented in which a delicate interaction between the genomic constitution and (gonadal) micro-environment (referred to GENVIRONMENT) is the actual determinant for the risk of an individual to develop a GCC, including those with a underlying DSD. An update on the current status of analyses will be presented.

Long-term outcome with a focus on growth, sexual development and fertility

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Forty-one phenotypic male and female patients with 45,X/46,XY mosaicism and 19 phenotypic male patients with Partial Androgen Insensitivity Syndrome (PAIS) were followed longitudinally in a single center. Preliminary data on 25 patients with 45,X/46,XY mosaicism and 14 patients with PAIS have previously been reported [1;2] with a primary focus on phenotype, growth and gonadal function.

Patients with 45,X/46,XY mosaicism can present with a wide spectrum phenotypically (from normal males to Turner-like females). Of the 32 patients raised as males, 24 had normal male phenotypes (External Masculinization Scores (EM scores) of 11.5 or 12). EM scores for the nine girls varied between 1 and 7.5. The females had their gonads removed due to the risk of cancer and therefore need life-long hormone replacement therapy. Fifteen of 16 males older than 13 years of age experienced spontaneous pubertal onset. Thus for the boys, whose gonads are not surgically removed, gonadal function seems to be sufficient for spontaneous pubertal onset. In the initial study, median height SD score was -2.0 (range -3 to 0.3) for males and -2.2 (range -2.5 to -1.4) for females. 45,X/46,XY mosaicism appears to be associated with short stature and patients seem to benefit from growth hormone therapy. Histology was abnormal in all available tissue samples (n=18). Five patients had carcinoma in situ.

Patients with PAIS can present as both undervirilized males and virilized females. We report on 19 male patients. EM scores ranged between 5 and 12. All patients experienced gynaecomastia during puberty. Impaired phallic growth was observed in five of 15 patients (four files lacked information). In the initial study, patients appeared to benefit from testosterone treatment both in terms of phallic growth and gynaecomastia. Furthermore, the median height SD score was 0.7 (range -2.1 to 2.1).

We thus report long term outcomes in terms of phenotype, growth and gonadal function in patients with 45,X/46,XY mosaicism and PAIS followed in our tertiary clinic. However, the heterogeneity of DSD patients does not allow for common conclusions on long term outcomes for all patients. Individual treatment and management is essential.

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Plenary: Care Across the Age Span

Vaginal hypoplasia in adolescents: Addressing multiple clinical needs in a sex-positive framework

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Background. In young women with vaginal hypoplasia, such as in Mayer-Rokitansky- Küster-Hauser syndrome (MRKH) and in Complete Androgen Insensitivity Syndrome (CAIS), surgical vaginoplasty and non-surgical self-dilation treatments are available to lengthen the vagina and facilitate sexual penetration activities. It seems that about an 80% success rate can be expected from any of the techniques. Using a more selective approach to surgery - in line with recommendations by the American College of Obstetricians and Gynecologists and DSD advocacy groups opposing to genital surgery if possible - it is estimated that only around 15% of patients who use the non-surgical approach will need to proceed to a surgical one. Reasons for failure, however, need further clarification.

Methods. We present the available literature on factors associated with long-term outcomes and compliance in vaginal dilation treatment, with recommendations for clinical practice.

Results and conclusions. Vaginal dilator treatment increases vaginal dimensions within the normal range, without major complications and regardless of start vaginal length or diagnosis (CAIS vs MRKH). Anatomical changes are associated with better psychosexual outcomes, at least immediately after treatment. Long-term outcomes remain scarce. In addition, some follow-up is limited to assessments of patency or penetration without considering the quality of sexual experience. Central to a sex-positive perspective is that sexual wellbeing also encompasses physical pleasure, intimacy and sexual self-efficacy, and

freedom from pain and negative affect regarding sexuality. In the few studies addressing these dimensions, long-term outcomes are not optimistic.

Above all, the results emphasize a need to look harder at the challenges of living with vaginal hypoplasia syndromes and care providers may need to investigate multiple clinical needs more thoroughly. Young women's sexual and emotional wellbeing as well as compliance with vaginal dilator therapy is influenced by a variety of psychosocial factors, including attitudes towards the dilator, values, beliefs, emotional adjustment to the diagnosis and motivations. The role of psychological interventions as well as peer support as both a primary and adjuvant treatment needs further evaluation.

Sex Hormones and cardiovascular health

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Future health and disease are determined by societal and biological factors affecting germ cells, the newborn and the adult. Men die earlier than women at all ages even if the gendergap has diminished recently. More miscarriages appear with the male fetus, more boys than girls die at birth, more boys are born with birth defects, during the teenage period to the age 40 more men than women commit suicide and are involved in homicide and other aggressive actions. In Europe 2014 cardiovascular disease (CVD) was the most common cause of death in men, 42 %, and women, 51%, but for breast cancer only 3 %. In a recent special issue about CVD in women (1) the editorial stated: "Compared with men, women have unique biological life events, which may alter their risk of cardiovascular disease and response to therapies. However, these events have largely been ignored in cardiovascular trials". Menopause and pregnancy are two such events." Women are still largely understudied. We still need women, female animals and female cells to be included in the trials as recommended by the NIH 2014 (2).The traditional CV riskfactors are the same for both men and women but don't have the same impact like diabetes and smoking being much more dangerous for the female heart. Special riskfactors for women are complications during pregnancy (pre-eclampsia, gestational hypertension –diabetes- obesity) and delivery .Not to breastfeed have recently been shown to be a risk for future CVD. Others are early menopause, PCOS and cytostatics for breast cancer (3).

No evidence exists that postmenopausal hormone therapy provides any protective effects against death from any cause, and specifically death from cardiovascular disease, non-fatal heart attacks or angina, either in healthy women or women with pre-existing heart disease. Instead the findings showed a small increased risk of stroke for post-menopausal women (4).

1. Circulation, Cardiovascular Quality and Outcomes (2015) Vol 8, number 2, suppl 1, March
2. Clayton JA, Collins FS, Nature (2014) vol 509, May 15
3. Schenck-Gustafsson K. Maturitas , 2009 Jul 20;63(3):186-90.
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Long term problems after male genitoplasties

Joao Luiz Pippi Salle, Sidra Medical Centre, Doha

Male genitoplasties are commonly performed in patients with DSD. This lecture will discuss generalities about male adolescents/young adults with DSD and the most common long term problems following male genitoplasties..The main technical faults leading to late complications as well as recent attempts to overcome them will be briefly discussed. Finally it will be emphasized the need of long term follow up of these population, ideally in well-structured multidisciplinary transition clinics.

Closing Guest Lecture

Sexual Health, human rights and law

Marleen Temmerman, WHO

Sexual health today is widely understood as a state of physical, emotional, mental and social well-being in relation to sexuality. It encompasses not only certain aspects of reproductive health – such as being able to control one's fertility through access to contraception and abortion, and being free from sexually transmitted infections (STIs), sexual dysfunction and sequelae related to sexual violence or female genital mutilation – but also, importantly, the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. Indeed, it has become clear that human sexuality includes many different forms of behaviour and expression, and that the recognition of the diversity of sexual behaviour and expression contributes to people's overall sense of well-being and health.

Developments over the past three decades, particularly in the wake of the HIV pandemic, have brought an understanding that discrimination and inequality also play a key role in whether or not people can attain and maintain sexual health. For example, those who are perceived as having socially unacceptable sexual practices or characteristics, such as being HIV-positive, being an unmarried sexually active adolescent, a sex worker, a migrant, a transgender or intersex person, or engaging in same-sex sexual behaviour, suffer both marginalization and stigma, which take a huge toll on people's health. Those who are deprived of, or unable to access, information and services related to sexuality and sexual health, are also vulnerable to sexual ill health. Indeed, the ability of individuals to achieve sexual health and well-being depends on their access to comprehensive information about sexuality, knowledge about the risks they face, vulnerability to the adverse consequences of sexual activity, access to good quality sexual health care, and access to an environment that affirms and promotes sexual health. As well as being detrimental to their sexual health, discrimination and inequalities may also constitute a violation of human rights.

The talk will focus on the relationship between sexual health, human rights and the law. Drawing from a review of public health evidence and extensive research into human rights law at international, regional and national levels, the report shows how states in different parts of the world can and do support sexual health through legal and other mechanisms that are consistent with human rights standards and their own human rights obligations.

Posters

P1

Communication With Peer Support Groups And Families - Results From An International Survey Of Specialist Care For DSD.

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Background: Communication amongst affected people and peer support groups (PSG) is important for optimal management in DSD. However, the extent of communication that occurs at the moment is unclear.

Methods: To explore the current models of communication and to determine the current involvement of PSG in DSD care, an international survey of 124 paediatric endocrinologists,, identified through DSDnet and the I-DSD Registry, was performed in the last quarter of 2014.

Results: A total of 77/124(62%) clinicians, working in 74 centres, and from 38 of 42 countries (91%) responded. In 21(28%) centres, parents/individuals with DSD meet locally. Of the 77 clinicians, 48(62%) reported that they are aware of at least one PSG and, in total, 78 discrete PSG were identified. In 82% of the cases the clinicians reported that they would recommend the reported PSG to the affected person with DSD. Of the 77 clinicians, 27(35%) reported collaboration with the multidisciplinary team (MDT) during the first three months after a new clinical presentation. In such a scenario, the availability of a PSG was reported as desirable but not available by 47(61%) of the clinicians. This group of 47 consisted of 24/48(50%) clinicians who were aware of at least one PSG, and 23/29(79%) of those not aware of any PSG ($p=0.008$). Discussions of the results of genetic tests with the family are lead by a paediatric endocrinologist in 73/77(95%) clinical teams. Other MDT members including a clinical geneticist, in 53/77(69%), and clinical psychologist, in 12/77(16%), participate in the discussion with the family. Additional information about the condition was provided to parents by face to face discussion(96%), clinic letters(44%), web-based resources(43%), paper leaflets(38%) and links with PSG(35%). In the communication and information reported to be provided by PSG, 50% was in local or national language, 45% in English and 5% in both national and English language.

Conclusion: Approximately 50% of paediatric endocrinologists in specialist DSD centres may involve or recommend a formal PSG. There is a need for greater awareness of the availability of local peer support for affected families as well as the benefit of this support.

Follow-Up Studies: The Good, The Bad, and the Ugly

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Follow-up studies have been conducted by numerous disciplines that in turn come to different conclusions about what is “best” for an individual who has Disorders of Sexual Development (DSD). More specifically, while individual and follow-up studies conducted by surgeons performing the various procedures find that their *results* are optimal and patients are *satisfied*, summaries and reviews of follow-up studies conducted by investigators outside the surgical specialty are generally less favorable. In addition only a few studies have included more in depth data collection of patient outcomes via patient reports of satisfaction and function.

The aim of this research is to critically assess the methodology utilized by follow-up studies in order to determine *who* (surgeons vs. patients) is actually *satisfied* with the results and how recommendations for and against surgery as well as timing of surgery are influenced by the differences in reporting.

The objectives are to provide a historical context for follow-up studies, making note of how follow-up studies have changed prior to and after the Consensus Statement of 2006, to tease out discrepancies between surgeons’ methodologies and other academics methodologies when reporting surgical outcomes, and how patient satisfaction is defined both methodologically and epistemologically by surgeons and other academics.

The methodology will consist of content analysis of over 100 peer reviewed journal articles.

In conclusion, our findings *to date* indicate that while surgeons are satisfied with the result of the surgery they perform, this is not confirmed by review articles, or patient satisfaction *surveys* via standardized questionnaires or interviews. We conclude that there is more need to conduct more “objective” long-term follow-up studies with focus on patients who had “normalizing” surgery regarding satisfaction with surgical results (cosmesis, function) as well as sexual satisfaction and function. There is a lack of long-term follow-up studies in particular for patients who had childhood surgery. Essentially what we are calling for is a more patient centered approach to surgery in DSD with increased consideration of long-term follow-up studies into patient satisfaction with an emphasis on function and psychosexual function.

P3

Sex Testing of Elite Female Athletes with DSD: Science and Controversies

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Between 1968 and 1999, the International Olympic Committee (IOC) required all female athletes to undergo genetic testing as part of its sex verification policy, under the assumption that it needed to prevent men from impersonating women and competing in female-only events. After critics convinced officials that genetic testing was scientifically and ethically flawed for this purpose, the IOC replaced the policy in 1999 with a system allowing for medical evaluations of an athlete's sex only in cases of "reasonable suspicion," but this system also created injustice for athletes and stoked international controversies. In 2011, the IOC adopted a new policy on female hyperandrogenism, which established an upper hormonal limit for athletes eligible to compete in female-designated events. This new policy, however, still leaves important medical and ethical issues unaddressed. We review the history of sex verification policies, discuss the situation of athletes with Disorders of Sex Development, and make specific recommendations on ways to improve justice for athletes within the bounds of the current hyperandrogenism policy, including suggestions to clarify the purpose of the policy, to ensure privacy and confidentiality, to gain informed consent, to promote psychological health, and to deploy equitable administrations and eligibility standards for male and female athletes.

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Title: Incorporating Support & Advocacy into the Disorders of Sex Development - Translational Research Network (DSD-TRN): Building Relationships and Resources for Patients, Families, and Healthcare Providers

Background: The DSD-TRN was launched in 2011 with the goal of extending discovery and identifying best practices in DSD care. The network governance structure assigns a leadership role to Accord Alliance, a non-profit promoting comprehensive and integrated approaches to DSD care. Accord Alliance is responsible for coordinating efforts of the Advocacy Advisory Network (AAN), a consortium of DSD patient support and advocacy organizations that advises on the clinical care and research conducted at the 10 DSD-TRN member sites across the US.

Aim/Objective: To highlight development and performance of the AAN, including leading projects and delivering resources disseminated throughout the network's clinics and beyond.

Results: The AAN, together with clinicians and researchers in the DSD-TRN, delivered a joint response to a *request for information* from the sponsor of the DSD-TRN (NICHD, National Institutes of Health) regarding institute research priorities. The AAN co-organized (with DSD-TRN clinicians and researchers) a conference for network members that resulted in the formation of three high priority workgroups: *Shared Decision-Making*, *Improving the Standard of Information* materials for affected families and their providers, and building *Transition Care* resources for patients with DSD aging out of pediatric healthcare. The AAN was instrumental in drafting a DSD Clinical Services Survey administered to all centers in the US reporting that they deliver pediatric care in DSD (manuscript in preparation). Progress in collaboration between patient stakeholders, clinicians and scientists has also seen tensions over the differential valuing of "personal experience" and "generalizable evidence."

Discussion: Creation of an AAN within the DSD-TRN reflects an aspiration for enhanced patient and family-centered care called for in the DSD Consensus Statement. Four years into this collaboration, substantial progress is being made, including improved understanding of contrasting perspectives regarding different forms of "evidence" and how they can be applied to modify clinical management. The DSD-TRN serves as a platform for standardizing

care and resources for families/patients across member sites, strengthening communication among stakeholders and increasing the likelihood that patients and families benefit from a broad range of educational, medical, and peer-support resources.

N. Delimata

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In his book, *A Treatise of Human Nature* (1739) David Hume articulated a problem which has dogged philosophers of science and ethics for centuries (Hume, 1969). He argued that it is not possible to ground an 'ought' (an evaluative or normative statement) with an 'is' (a physical thing or event). While most fields of science regard this dualism as nearly axiomatic (Lisska, 1996), biomedicine is a paradigm instance where is and ought, or facts and values, intersect through concepts such as 'disease', 'disability' and 'disorder' (Kincaid and McKitrick, 2007). Hume was not suggesting that it is not possible to make an evaluative statement about a physical thing; rather, the statement or term must first be grounded in an evaluative premise. For Hume, all evaluative premises are grounded in emotional experience and are therefore subjective. Some fields of knowledge have found this proposition to be problematic because this relativized knowledge means that evaluative or normative statements or terms are always open to question. Within biomedicine some philosophers have attempted to overcome this relativism and have sought to ground normative/evaluative statements through critical realism (Hull, 2006), selectionism (Ayala, 1998) or functionalism (Perlman, 2010). This presentation will explore several methods that might be used to ground the evaluative / normative term 'disorder of sex development' and examine whether Hume's is/ought dualism continues to contest such a term. It will conclude that the term 'disorder of sex development' has no universal application and argue that if the term is to be validly applied to individuals it must be relative to their experience.

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P6

Title: Body Image and Quality of Life (QoL) in women with Congenital Adrenal Hyperplasia – outcomes and avenues for adjuvant treatment

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Abstract

Congenital Adrenal Hyperplasia (CAH) is a lifelong disease, often requiring medication, surgery and the end result may still be not ideal, with many women unhappy with their life and body. Whilst research into CAH often focused on health related function and gender identity, this research focuses on assessment of Body Image and Quality of Life. With the aim to help better understand outcomes, the problems faced by these young women, and how we as healthcare providers can find ways to reduce the negative impact of this condition.

With the aid of a cohort of 47 CAH women in Malaysia and controls with diabetes we have started some of the research. We used the BIQLI questionnaire and correlating with age of diagnosis and surgery, type of feminising surgery, and other features of virilisation.

There were no statistically significant differences between our CAH and DM groups. But, when analysed in isolation, the CAH group showed significant differences in their self-image and QoL based on their level of virilisation, but no differences based on their age of diagnosis, surgery, or type of feminising genitoplasty. Physical repercussions of poor CAH control correlated with negative body image and negative views of interactions with other people of their own sex. Better CAH control and Rx of acne and hirsutism may lead to better body image, life satisfaction and positive outcomes for these women.

Psychosocial well-being in Dutch adults with a disorder of sex development

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Background

Atypical sex development is associated with social stigma and shame. Few studies have been conducted on how psychosocial well-being of individuals with DSD may be differentially affected when controlling for gender and degree of genital atypicality.

Hypothesis: patients with atypical genitalia are most vulnerable and prone to develop emotional problems.

Methods

Follow-up audit.

Patients with DSD, aged 14-60 years, stratified in three subgroups according to self-identified gender and genital atypicality; 1. 46,XY women born with female appearing genitalia (women FG, n= 35); 2. 46,XY and 46,XX women born with atypical genitalia (women AG, n= 69); 3. 46,XY and 46,XX men born with atypical genitalia (men AG, n= 16).

Measures: Rosenberg Self Esteem Scale (RSES), Adult Self-Report (ASR – emotional/behavioural problems, psychopathology), a fatigue questionnaire (CIS), a health-related quality of life questionnaire (TAAQOL). For all measures reference data were available.

Mann-Whitney, Wilcoxon signed-rank and Kruskal-Wallis tests were applied.

Results

RSES: Individuals with DSD reported a low self-esteem (men p=.001, women p<.001)

ASR: Women with DSD scored below the cut-off scores for psychopathology. Women AG reported more problems than women FG and the reference group on the social isolation (p=.02), attention and hyperactivity (p <.001), aggression (p=.04), rule-breaking behaviour (p=.01), and antisocial behaviour (p <.001) scales.

CIS: All women with DSD reported increased feelings of fatigue (p< .001).

TAAQOL: No differences between groups on most scales. Women with DSD reported memory/concentration problems (p < .001) and greater happiness (p=.046) than the reference group. Men AG: no differences on ASR, fatigue, and TAAQOL compared to the reference groups.

Conclusions

Patients with DSD reported a good quality of life and no psychopathology. However, women born with atypical genitalia indicated significantly higher levels of emotional and behavioral problems than women from other groups. All women reported elevated levels of fatigue and both men and women reported low self-esteem. The current study indicates that, in women, psychological distress is associated with atypicality of the genitalia. Additional attention to more detailed aspects of psychological well-being in DSD is needed. Individuals with DSD and their families should have access to a wide range of information, counseling and comprehensive care.

Psychological consequences for DSD patients with Y chromosome

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Background

Disorders of sex development (DSD) are the most difficult diagnostic and therapeutic problems because of the lack of clear and common standards in this area. The specificity of DSD has psychological consequences for the patient and for his family. One of the major challenges is decision about official sex.

Aim

The aim of the study was assessment of quality of life and the differences in the functioning of men and women.

Methods

The presented study included 60 patients with DSD, all with Y chromosome, aged 15-65 years: 48% women and 52% men. The following tests were used: *Psychological Sex Inventory*, *The Rosenberg Self-Esteem Scale (SES)* and *Multidimensional Self-Esteem Inventory (MSEI)*. Student's *t*-test or Mann-Whitney *U* test were used for the statistical analysis.

Results

Women had significantly lower self-esteem ($t=-2,016$; $p=0,048$). In the test evaluating gender identity (psychological sex), study group compared with the control group had significantly lower rates of femininity ($t=-2,72$; $p=0,007$). Patients after genital surgery had significantly more indications to take psychological or psychiatric care than patients not operated. They had significantly more distressing symptoms: somatic symptoms, daily functioning disorders, depression, feelings of anxiety and insomnia ($Z=1,985$; $p=0,047$). Patients exposed to jokes because of illness had significantly lower self-esteem of physical (sexual) attractiveness ($t=-2,123$; $p=0,038$) than patients not exposed. Patients declaring that their sex life is limited because of illness, had significantly lower life satisfaction ($t=-2,965$; $p=0,005$) and lower self-esteem of physical (sexual) attractiveness ($t=-2,432$; $p=0,019$) than patients with unlimited sex life.

Conclusions

Disorders of sex development can be the cause of psychiatric disorders: depression, anxiety or insomnia. These diseases can significantly lower self-esteem and belief in own physical and sexual attractiveness. Particularly at risk are patients exposed to ridicule and stigmatization. The presented study showed also worse functioning of women than man. Patients with DSD and the Y chromosome have fewer female characteristics in the meaning of psychological sex.

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Health care-seeking behavior in late-identified patients with congenital adrenal hyperplasia (CAH) in Central Java, Indonesia

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Background

In many Western countries, patients with congenital adrenal hyperplasia (CAH) are identified soon after birth and receive medication soon after identification. In our center, many patients were referred late in adolescence or adulthood. Many psychological problems were identified among these late-identified patients and highlight the importance of early referral for prevention. However, it remains unclear why parents of children with CAH decided not to seek healthcare professionals soon after birth, or adolescents and adults wait until later in life. This study aims to identify characteristics of late-identified patients with CAH and explore their reasons to delay in seeking medical treatment.

Results

We compared a group of late-identified patients with CAH (first referral age > 1 yrs ; n= 44) to a group of early-identified patients with CAH (first referral age 0-1 yrs; n= 28) in view of age at first visit, birth attendant, referral, distance from home to medical center, parental educational background, parents' occupations, and reasons for help-seeking. Data were collected using interview during clinic visits and phone survey. The majority of parents of late-identified patients with CAH had lower educational background than parents of early-identified patients. The birth attendant and referring person play an important role in influencing parents of children with CAH in making decision to seek medical help. The majority of adult patients or parents of children with CAH delayed seeking medical help due to various reasons, including lack of knowledge about CAH and possibility of treatment, poverty, religious beliefs, genital appearance, which leading to lack of awareness and initiative to seek help.

Conclusion

Education about CAH and the importance of early referral should be promoted widely among health practitioners (particularly midwives). Moreover, the consequences of delayed treatment should be explained to local religious leaders and local government officers who can endorse the affected person to seek medical treatment. It is necessary to provide educational material in written and in simple language containing medical, psychological, socio-cultural, and religious aspects related to CAH, to promote their awareness about CAH and to retain their knowledge about CAH.

P10 The body image and genitalia appearance concerns and virilization features of CAH female patients in Malaysia

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Background

Due to a paucity of published data, a study was undertaken to investigate outcomes of patients with Congenital Adrenal Hyperplasia (CAH) raised as females in Malaysia, with specific outcomes compared to a control group of diabetic female patients. This presentation will discuss the comparative outcomes of body image and genital appearance perceptions and virilization features only noted in the CAH group. To assess body image and genitalia appearance concerns, the translated and validated Bahasa Malaysia version of the Body Image Disturbance Questionnaire (BIDQ) was used.

Results

This was a descriptive, cross-sectional study of 59 CAH female respondents in Malaysia, mean (SD) age was 16.3 (± 4.2) years, age range 10 – 28 years. There were 57 female diabetics forming the control, group, mean (SD) age was 16.5 (± 3.4) years, age range 10-26 years. There were no statistical differences in terms of age, religion, education level, occupation and family incomes.

The BIDQ was completed by respondents ≥ 13 years old. From the results of the first part of the BIDQ which evaluated if there were any concerns regarding unattractive body parts , there were more controls who had concerns (n = 29 / 49; 59.2%) compared to CAH respondents (n = 19 / 44; 43.2%) ($p=0.18$). From the results of the second part of the BIDQ evaluating genitalia appearance concerns, there were more CAH respondents with concerns (n = 12 / 40; 30.0%) compared to the controls (n = 6/ 43; 14.0%), ($p = 0.13$). Significantly more CAH respondents found these genitalia concerns distressing (CAH: n = 12/ 40; 30.0% vs controls: n = 4/ 43; 9.3%, $p < 0.05$).

The virilization features consisting of deep voice, hirsutism, acne, masculine physique and darker skin pigmentation were noted among the CAH patients. More than a third of CAH patients (35.6%) had at least one virilization feature. Five CAH respondents (8.5%) had all five features.

Conclusion

The CAH respondents had more concerns regarding the appearance of their genitalia compared to the controls. Presence of virilization features can be used to indicate poor control of androgen levels in CAH patients.

Islamic perspective of DSD and gender-related issues

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Background

One of the controversies in the management of patients with disorders of sex development (DSD) is regarding the optimal gender assignment. Difficulties arising from this issue include timing of decision of gender assignment, who should be involved in making the decision, disclosure and what happens if the patient requests for gender reassignment. Islam recognizes the existence of the Khuntha, defined as an individual with both male and female genital organs or one who has neither. Two cases of Muslim patients with DSD requested for gender reassignment in Malaysia.

Results

The first patient was an 18-year old patient with Congenital Adrenal Hyperplasia (CAH) raised female, requesting for reassignment to the male gender. The second patient was a 27-year old lecturer, unknown diagnosis of DSD, already underwent feminizing surgery, raised male and requesting gender reassignment to the female gender. Both cases were presented to the religious authorities at the Department of Islamic Development in Malaysia. Both underwent several sessions with psychiatrists to evaluate their psychosexuality. Investigations were extensively performed on the second case to determine the diagnosis and to confirm if this patient was a true DSD. Discussions between the medical professionals involved and the religious scholars were held over several sessions in order to come to the best decision regarding this request for gender reassignment. Islamic rituals such as prayer (Solah), covering of the parts of the body in public or to non-family members (aurat), inheritance laws, marriage obligations and bathing rituals of the deceased differ according to Islamic jurisprudence by gender. Different schools of Islamic jurisprudence differ in their rulings on these gender-related issues where the khuntha is concerned. Muslim patients with DSD who request gender reassignment thus need to be aware of these issues regarding Islamic jurisprudence.

Conclusion

As Islamic rituals and obligations are an important part of the daily life of Muslim DSD patients and their families, in order to enable holistic care in their management and enable adaptation in their communities, religious authorities need to be included in the multidisciplinary team in their management. (339 words)

"We are also humans we who are sick"

Experiences of 13 women with congenital adrenal hyperplasia

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Background

Various aspects of living with congenital adrenal hyperplasia (CAH) such as quality of life, psychosocial adaptation, atypical gender behavior, and long-term outcomes of treatment and surgery have been extensively studied in women with CAH. However, qualitative research exploring individual experiences of living with CAH is scarce.

Results

Interviews with 13 Swedish women with CAH (ages 18-54, with different genotypes and phenotypes) were analysed by qualitative content analysis revealing seven categories: experiences of being a patient, acquiring knowledge, sharing information, being subjected to research, exploring relationships and identities. Two latent themes were formulated from the latent content of the interviews - a struggle against shame and a search for self. For some women, CAH had had a large impact on all parts of life and constituted a hinder when, for instance, forming relationships. For others, CAH was described as a side issue in their lives. The struggle against shame is manifested as a battle to be seen as individuals and CAH was considered one part of their lives and *not all they are*.

Conclusion

From these results it can be argued that the women could have benefitted from more psychosocial support, increased sexual education, a deeper understanding of CAH along with more information during transitions such as puberty, intimate relationships, and childbearing. Shame may be counterbalanced by increased parental support, efforts directed at providing children with CAH with a language for their condition, and continuous support during upbringing.

Multidisciplinary and psychosocial shift in DSD/Intersex management

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Background

Nowadays, management of DSD/intersex in Spain follows current European and American clinical standards. At the core of these new standards of care is a plea for multidisciplinary teams (MDTs) composed ideally by «paediatric subspecialists in endocrinology, surgery or urology, psychology/psychiatry, gynaecology, genetics, neonatology, and, if available, social work» (Lee *et al.*, 2006). Equally, these new standards of care defended a patient centred model that introduces a psychosocial shift in health care attention for DSD patients.

Discussion

If we agree that most problems and obstacles DSD patients' and families' face are related with a social understanding of sex, gender, bodies and identities as a binary construction, how should MDTs intervene in health care practices for people affected by DSD according to this patient-centred psychosocial paradigm? In this paper we propose the need to consider health care at two different levels, responding to two different types of needs that may require two different types of teams. Current MDTs working in medical centres and composed by all the clinical specialities should be distinguished from what we call a Transdisciplinar Team (TDT), less concerned about the professional label people come with than with the critical and interdisciplinary knowledge they produce. Current MDTs' main functions are achieving proper diagnosis, improving treatments and surgeries, and controlling potential medical complications. New proposed TDTs should respond to the «psychosocial paradigm shift» demands encouraging active patients participation -who should get recognition to their own expertise based on experience. Transdisciplinar knowledge mobilised in TDTs should include a range of different skills to respond to patient needs: from knowledge of the physiological particularities of each condition, to specific training in communication and gender. Whereas this team would not deal with molecular diagnosis, it would certainly be more accurate in answering the demands of people with DSD and their families.

TDTs would not necessarily have a concrete inter- or multidisciplinary organization. TDTs are intended as a decentralized model where Information and Communication Technologies and SG are fundamental for care practices. TDTs do not need to work inside hospitals. In fact there are already some initiatives around the figure of the «patient navigator» as a member of a healthcare team that helps patients to «navigate» the healthcare system, coordinating patient attention, connecting patients with resources, and helping patients understand the healthcare system.

THREE NOVEL CYP21A2 MUTATIONS IDENTIFIED IN BRAZILIAN PATIENTS WITH 21-HYDROXYLASE DEFICIENCY: A SINERGISTIC EFFECT.

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Background

The 21-hydroxylase enzyme is essential for cortisol biosynthesis. Its deficiency leads to androgen excess, consequently, to virilization and rapid somatic growth with accelerated skeletal maturation. Mutations in *CYP21A2* are responsible for different forms of 21-hydroxylase deficiency resulting in different phenotypes observed in Congenital Adrenal Hyperplasia, depending on how they affect the protein production or the enzyme activity. The aim of this study was to investigate *in vitro* three novel *CYP21A2* mutations, separately and in combination, as identified in our patients and correlate with the clinical form of the disease.

Results

Three novel mutations were identified in two families. One affected boy was compound heterozygous for the splice mutation c.290-13A/C>G and p.Ile172Asn combined with the novel mutation p.Val358Ile, inherited from his mother and father, respectively. He was diagnosed with the salt wasting form of Congenital Adrenal Hyperplasia. Both novel mutations p.Asp377Tyr and p.Leu461Pro have been identified in a second female child carrying p.Val281Leu in compound heterozygosity, inherited from her mother and father, respectively. She presented premature pubarche since 5 years old and when she was 6 years and 4 month old her bone age was 8 years and 7 months. Preliminary *in vitro* studies indicated that p.Asp377Tyr, p.Leu461Pro and p.Val358Ile are compatible with the non-classical form of Congenital Adrenal Hyperplasia presenting 79%, 31% and 59% of residual activity (conversion of 17-OHP to 11-DOF), respectively. When tested in combination, the mutations p.Asp377Tyr+p.Leu461Pro and p.Ile172Asn+p.Val358Ile presented synergistic effects, resulting in 10% and 0% of residual activity (conversion of 17-OHP to 11-DOF) respectively.

Conclusions

It is known that combinations of mutation in *CYP21A2* gene can result in a synergistic effect of enzyme activity, as can be observed on data presented here. Interestingly, two novel mutations were identified in the same allele. Preliminary results for *in vitro* studies on enzymatic activity allowed the correlation between phenotype and genotype of all patients. However, more experiments will be performed to validate those data.

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FGFR2 MUTATION IN XY SEX REVERSAL WITH CRANIOSYNOSTOSIS

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46,XY gonadal dysgenesis (GD) is a spectrum of genetic disorders of testis development largely of unknown etiology. Associated genital anomalies range from hypospadias to complete male-to-female sex reversal. We and others showed that FGFR2 is required for testis determination in mice, rendering human *FGFR2* a candidate gene for unsolved 46,XY GD cases. However, while *FGFR2* mutations cause LADD and various craniosynostosis syndromes, testicular defects were not described. Here, we report the first *FGFR2* mutation in 46,XY GD. The 15-year-old phenotypic female presented with delayed puberty and dysgenic gonads lacking testicular tissue. In addition, the patient was diagnosed with Crouzon-like syndrome based on craniosynostosis, brachycephaly, proptosis, and downward slanting eyelids, and also exhibited elbow/knee contractures and short stature. Sequencing *FGFR2* identified the heterozygous missense mutation, c.1025G>C (p.C342S), affecting the 2c isoform. C342 substitutions for S or other amino acids (R/F/W/Y) occur frequently in Crouzon syndrome leading to constitutive receptor activation. A ‘knock-in’ mouse model of Crouzon syndrome carrying the C342Y substitution (*Fgfr2c*^{C342Y/C342Y}) showed disrupted testicular development with loss of the androgen-producing Leydig cells, consistent with 46,XY GD and sex reversal in the patient. To reveal mutant receptor activity, we generated *Fgfr2c*^{C342Y/-} mice which showed XY gonadal sex reversal, thus loss-of-function. In summary, a novel form of craniosynostosis with XY sex reversal arising from an *FGFR2c* mutation was identified. The effect of the C342S substitution appears cell context dependent, activating FGFR2c in the skull and inactivating FGFR2c in the developing gonads. Diagnosis of 46,XY GD should be widened to encompass FGF-signalling components.

FGF9 ACTIVITY FROM NORMAL MALES AND A 46,XY FEMALE

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Disorders of sex development (DSDs) include 46,XY gonadal dysgenesis (GD), where a specific molecular diagnosis is made in only ~30% of patients. Improved understanding of the genetic causes of DSD will lead to better diagnosis and management. Many GD genes are involved sex determination and interact agonistically or antagonistically.

FGF9 is expressed in Sertoli cells and is critical for testis determination in the mouse since *Fgf9*-/- mice show partial or complete XY gonadal sex reversal. In the developing XY gonad FGF9 maintains SOX9 expression indirectly through repression of Wnt4. However, the mechanism of Wnt4 repression by FGF9 is still unknown. We have established an *in vitro* assay system of FGF9 function during foetal gonadal development to identify the signalling pathways involved in Wnt4 repression. We show that FGF9 treatment of the mouse Sertoli cell line 15P-1 can efficiently down-regulate Wnt4 expression in a dose dependent manner. Cycloheximide treatment inhibited Wnt4 repression, suggesting that FGF9 requires new protein synthesis to down-regulate Wnt4. FGF signaling activates four major signalling pathways; MAP Kinase, AKT, STAT, and the PLC γ . To determine which pathways are involved in FGF9 repression of Wnt4, we treated 15P-1 cells with drugs to these pathways. Drugs blocking the ERK1/2 and JNK pathways significantly inhibited Wnt4 repression, suggesting that FGF9 down-regulates Wnt4 via the ERK1/2 and JNK MAPK pathways, but not via p38 MAPK pathway. *Ex vivo* experiments are underway.

Despite the strong evidence for a role of FGF9 in mouse sex determination, no FGF9 mutations had been identified in DSD. Here, we describe the first FGF9 mutation in a patient with 46,XY GD, a maternally derived heterozygous single nucleotide substitution. Biochemically, the substitution is predicted to interfere with FGF9 dimer formation, whose function is contentious. Recombinant wildtype and DSD mutant FGF9 protein is being produced and purified for testing in our Wnt4 repression assay *in vitro*, and in gonad cultures *ex vivo*.

P17

Characterization of mutations in the androgen receptor (AR) identified in 38 Brazilian families with complete or partial androgen insensitivity syndrome (AIS)

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BACKGROUND: Androgen insensitivity syndrome (AIS) is a genetic disease X-linked, with functional abnormalities of the androgen receptor (AR). Mutations in RA are associated with phenotypic spectrum, which can present complete insensitivity (CAIS) or partial insensitivity (PAIS).

OBJECTIVES: To characterize the mutations identified in AR in 38 Brazilian families with AIS. Sort the mutations identified in the type, location in the gene, associated functional domain and associated phenotype.

METHODS: PCR amplification of the coding regions and promoter of the AR gene, followed by direct sequencing. The identified mutations observed in literature, genomic sites and prediction sites. We classify mutations according to type (missense and nonsense), located in the gene (exon), the affected functional domain (NTD, LDB, DBD, Hinge) and phenotype (CAIS and PAIS).

RESULTS: We identified 17 different mutations in the AR in 22 families with PAIS (37 patients) and 13 in 16 families with CAIS (n = 23). Of these, 6 (CAIS) and 8 (PAIS) have not been described. Missense mutations were identified in 90.5% of PAIS and 83% of CAIS and nonsense mutations in 9.5% PAIS and 17% in CAIS. The location in exons were different in frequency between CAIS and PAIS, being more frequent in exons 5 and 7 (18% and 17%) in PAIS and in exons 1 and 4 (27% and 21%) in CAIS. As for distribution in functional domains, there was a lower frequency of mutations in the DBD domain (12.5% CAIS and PAIS 20%), followed by the NTD domain (CAIS 25% and 20% PAIS) and more in the LBD (62 , 5% and 60% CAIS PAIS). We describe for the first time, a large deletion in the promoter region in a family with PAIS, whose exonic region was normal. Not identified mutations in 18.2% of families with PAIS (4/22) and 6.25% of families with CAIS (1/16).

CONCLUSIONS: The identification of mutations related to different phenotypes of AIS in Brazilian families allows for greater insight into genetic defects in our patients. The strategy of seeking mutations in the promoter region, when there is clinical suspicion of AIS without mutations in exonic region of the AR was appropriated.

Sex chromosomal Abnormalities in Egyptian DSD patients

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Abstract

Background

Sex chromosome DSD constitute an important category in the definition of DSD. The study was conducted over a period of four years on DSD patients presenting to the outpatient clinic of NRC. The study included 379 patients comprising a wide spectrum of presenting features, associated with different arrays of chromosomal abnormalities. Patients were subjected to detailed clinical examination, pubertal staging, cytogenetic and FISH analysis. Laparoscopy with gonadal biopsy and FISH on gonadal tissue cells were done when indicated.

Results

The most commonly presenting feature was ambiguous genitalia (116 patients) followed by male infertility (97 patients). Short stature associated with TS phenotype was detected among 67patients. Patients presenting with primary/secondary amenorrhea constituted 43 of the patients, while multiple congenital anomalies or dysmorphism associated with genital anomalies was found in 28 patients. Other complaints included hypogonadism, undescended testis, female infertility and secondary amenorrhea.

Abnormal sex chromosomal constitution was found in 188 patients (49.6%). They included both numerical and structural sex chromosomal abnormalities. The most common numerical abnormality was 47,XXY followed by 45,X which had occurred in a pure form or in mosaicism with one or more cell lines. Structural sex chromosomal abnormalities showed a wide range of variability. The most common structural abnormality was iso(Xq), which was detected among 31 patients presenting with short stature or primary amenorrhea. Isodicentric Y abnormality was detected in 9 patients. Other Sex chromosomal abnormalities included X;Y translocation, Y;19 and Y;14 translocation, ring X, add (Xq), dup (Xp) and del (Xp). XX testicular DSD with SRY translocated to the Xp was found in 4 patients, one of them presented with Down syndrome.

Conclusion

This study confirms the dosage effect of sex chromosomes on somatic development and the phenotypic diversity of their presentation among different age groups.

Functional Analysis of three *NR5A1* mutations identified in patients with 46,XY DSD

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Background

Steroidogenic factor-1 (SF-1), denominated as nuclear receptor subfamily 5 group A member 1, is a protein that regulates several steps of adrenal and gonadal development. It is encoded by the *NR5A1* gene. SF-1 regulates a number of genes essential for normal reproductive physiology and endocrine function and it is highly expressed in steroidogenic tissues. Mutations in *NR5A1* have been found in a large number of 46,XY individuals with disorders of sex development (DSD) and can be associated with bilateral anorchia, isolated hypospadias, male infertility, and in some cases of adrenal tumors and endometriosis.

Results

Three mutations identified in SF-1 DNA-binding domain (DBD) have been analyzed to estimate their functional influence on SF-1 transcriptional activity. The p.C65Y and p.R39C were identified in 46,XY DSD idiopathic patients and the p.S32N was identified in a patient with 46,XY partial gonadal dysgenesis. Luciferase assays were performed using *AMH* and *STAR* promoters, and in all the cases, SF-1 mutants drastically reduced the transactivation of both promoters. Electrophoretic mobility shift assays (EMSA), used to investigate SF-1 DNA binding ability, have shown that the three SF-1 mutants are unable to bind to specific DNA sequences.

Conclusions

SF-1 DBD is essential to stabilize DNA binding and also is involved in nuclear receptor specific recognition of DNA target sequences; it has two zinc fingers and a FTZ-F1 box, which is essential for binding to DNA with high affinity. In this study we describe three mutations that lies in critical parts of DBD: p.S32N is located at the P-box of the first zinc finger; p.C65Y occurs at a zinc-coordinating cysteine at the second zinc finger and p.R39C was identified at a conserved arginine between both zinc fingers. Therefore, it is possible to predict that such amino acid changes would destabilize the zinc-finger conformation, affecting the protein translation, even without functional studies. *In vitro* analysis confirmed that they eliminate the activity towards target promoters due to DNA-binding impairment, as it was expected. The results elucidate the impact of these mutations in protein expression, justifying the DSD phenotype in each case.

P20

New case of androgen insensitivity syndrome due to A645D mutation of AR gene associated with short polyglycine and long polyglutamine repeats.

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Background

Androgen Insensitivity Syndrome (AIS) is an X-linked disease characterized by variable defects in virilization of 46,XY individuals due to mutations in Androgen Receptor (AR) gene, resulting in abnormalities of molecular pathways of androgen action. There is a complexity of phenotypic presentation of AIS with difficult genotype/phenotype correlation. Isolated A645D mutation has been described in patients with partial AIS (PAIS) and in a boy with a normal phenotype, but A645D mutation associated with short polyglycine (poliG) and long polyglutamine (poliQ) repeats was described by Werner et al. in two 46,XY patients with PAIS confirming the impact of the genetic variations affecting the polymorphic repeats on AR function and phenotype.

Clinical Report

Newborn by consanguineous parents (second degree cousins) with ambiguous external genitalia corresponding to grade 2b AIS according to Sinnecker classification: micropenis (1,8 cm stretched penile length), penile hypospadias, bilateral cryptorchidism. Karyotype 46,XY, SRY + with normal sequence. Müllerian structures were visualized with MRI. At 3 months of age: LH 12,88 IU/L; FSH 7,44 IU/L; testosterone (T) 6,9 nmol/L as in minipuberty; T/Δ4A 5,25; T/DHT 9,5; and T significantly increased to 27 nmol/L after hCG stimulation. No genetic variations of both type II 5α-reductase (SRD5A2) and SF1 (NR5A1) genes were found. Analysis of the AR gene revealed a A645D substitution in exon 4 associated with a long poliQ(29) and a short poliG(10) repeat in exon 1. The mother resulted a carrier for this particular AR allele.

Conclusions

Parental consanguinity and T/DHT ratio in our patient could suggest a deficit of 5α-reductase 2, but molecular genetic analysis of SRD5A2 gene was normal. Analysis of AR gene, instead, demonstrated a A645D mutation within the hinge region that has been also described in normal males. The study of poliG and poliQ repeats showed a pattern of short poliG(10) and long poliQ(29) that modulates AR activity in vitro in association with the A645D mutation, as described by Werner et al. The identification and description of our patient, as well as other additional DSD patients with this complex mechanism of gene expression regulation, may contribute to understand genotype-phenotype correlations in AIS.

P21 Chromosomal and molecular studies in a cohort of 88 patients with Disorders of Sex development.

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Background

Under the term Disorders of Sex Development (DSDs) are included all the medical conditions characterized by an atypical chromosomal, gonadal or phenotypical sex. They result from the disruption of any of molecular signals that control the accomplishment of sexual dimorphism. Due to the fact that mechanisms involved in sex development have to be fully elucidated, nowadays, the genetic defect causing a disorder of sex development may remain undefined in many cases, in particular with gonadal DSDs. The authors describe the clinical, cytogenetics and molecular findings of 88 patients with DSDs.

Results

We studied a cohort of 88 patients including 55 paediatric and 33 adult cases affected by different DSDs, afferent at the DSDs Multidisciplinary Centre of San Camillo-Forlanini Hospital, Rome (Italy). We characterized the genetic alteration in 56/88 (64%) of them. Five/88 patients showed an aberrant karyotype with mosaicism involving sex chromosomes. Between the patients with 46,XX DSD we identified two cases with *SRY* gene translocation to chromosome X, one patient with an heterozygous duplication involving *SOX9* and one individual with a *RSPO1* homozygous mutation (disorders of ovarian development). Fourteen patients with a 46,XX DSD due to androgen excess were affected by congenital adrenal hyperplasia due to *CYP21A1* alterations, while in one patient the *CYP11B1* was recessively mutated. In two women in whom the Mayer Rokitansky Küster Hauser syndrome was clinically diagnosed, partial duplication of the *SHOX* gene was found. The study of our cases with 46,XY DSDs identified the responsible gene in 6 individuals in whom the defect was gonadal (1 case=*NR0B1*; 1 case=*SRY*; 3 cases=*NR5A1*, one case=*DMRT1*) and in 24 patients with a disorder in androgen synthesis or action (15 cases=*AR*; 8 cases = *SRD5A2*; 1 case=*AMH*).

Conclusions

Our results highlight the genetic heterogeneity existing in each category of DSDs and further confirm that molecular characterization cannot be reached in a consistent number of cases. We believe that ingoing massive parallel sequencing techniques will permit to identify the genetic causes underlying these conditions in a greater number of patients.

Gender Re-assignment of a 46,XY-DSD Patient Associated with P450 Oxidoreductase Gene (POR) Mutation and Antley-Bixler Syndrome

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Background Cytochrome P450 oxidoreductase (POR) deficiency is a recently discovered new variant of Congenital Adrenal Hyperplasia. Clinically, POR deficiency is characterised by genital features a sexual development disorder (DSD), adrenal insufficiency and cranial-skeletal malformations described as Antley Bixler syndrome (ABS). Here we report a 46,XY-DSD patient with POR deficiency and gender (re)assignment to male. Clinical findings of the patient, laboratory characteristics and the medical and surgical treatments are presented, and the rationale of our decision are discussed.

Case report A 14-month old baby who had consanguineous parents was born phenotypically female with SRY positive, 46,XY-DSD (micropenis, pseudovaginal-perineal hypospadias and bilateral undescended testes). He was named and reared as female. He had midface hypoplasia, proptosis, hypertelorism, a depressed nasal bridge, low set ears and brachycephaly. There was limitation of supination and elbow extension, but no radiologically apparent synostosis. The diagnosis of POR deficiency was made with p.P399_G401del mutation, together with the clinical features of ABS. Gender (re)assignment to male was attempted with androgen replacement, proceeding with genitourinary reconstruction and psychosocial support.

Conclusion The P450 oxidoreductase deficiency causes decreased production of androgens, resulting severe male undervirilisation. Individuals with Antley–Bixler syndromic features, presenting with DSD should be analyzed for P450 oxidoreductase deficiency. Although technically challenging, appropriate surgical treatment should be performed to achieve acceptable gender.

A NOVEL WT1 GENE MUTATION THAT AFFECTS THE SPLICING ONLY OF THE -KTS ISOFORM IDENTIFIED IN A BOY WITH 46,XY DSD AND NORMAL RENAL FUNCTION

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Background

Wt1, one major regulator of gonadal development, acts as activator/suppressor and its function is complicated by the several different isoforms produced by a combination of alternative translation start sites, splicing and RNA editing. The insertion/omission of 3 residues produces the variants WT1 -KTS and WT1 +KTS. WT1 mutations have been described in 46,XY DSD phenotypes with associated kidney diseases or in isolated forms (hypospadias/cryptorchid testes; partially/complete gonadal dysgenesis). Here we report the study of a 46,DSD boy with a novel particular WT1 mutation.

Case report

First pregnancy, born at term to healthy non consanguineous parents. Prenatal karyotype (46,XY) discordant with phenotype at birth: micropenis, penoscrotal hypospadias, bilateral cryptorchidism. Sex assignment: male. Minipuberty hormonal investigations: T=1,1ng/ml. Cystourethrography: bilateral VUR IV-V grade. Laparoscopy: abdominal gonads with testis-like structure, müllerian remnants. Surgical treatment of VUR and hypospadias at 7mo. The patient was sent to our attention for endocrine/genetic evaluations at 3.5y of age before gonadectomy. Hormonal investigations: basal/stimulated T<0,02ng/mL (Gonasi 3000IU/m2/die 3 days); FSH 2,33mIUI/mL; LH 0,13mIUI/mL; SHBG 107.4mMol/L; basal cortisol/ACTH normal.

Mutational analysis: *NR5A* normal; *WT1*: heterozygous substitution (maternal) chr11:32413525T>A that affects the “T” of IVS9 donor splice site used for the -KTS variant. The +KTS variant is not affected, as the involved “T” is included in codon Gly475 without changing its sense. Subsequent evaluations: normal renal function without laboratory/clinical findings of nephrotic syndrome in the patient; isolated proteinuria in the mother (503 mg/day); creatinuria 60 mg/day.

As far as we know, this is the first human mutation affecting the -KTS variant only: as it interacts with SF1 on the AMH promoter, a -KTS reduction may results in an altered AMH expression and/or in disgenetic XY gonads. 46, XY -KTS KO mice show gonadal dysgenesis and renal hypoplasia, but deeper studies are necessary to understand the implications of this particular type of mutation in humans in heterozygous condition.

Conclusion

This report enlarged the spectrum of *WT1* gene mutations and confirms the importance to perform *WT1* gene analysis in 46,XY DSD cases with hypospadias and criptorchidism in order to undertake more appropriate therapeutic strategies and follow up also for the 46,XX carriers.

The Fuzziness of Next Generation Sequencing Analysis: A Case Study on DSD Patients in Australia

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Abstract

Computational bioinformatics workflows are extensively used to analyse data. With the unprecedented advancements in genomic sequence technology and opportunities for personalised medicine it is essential that results of analysis are repeatable by others, especially when moving into the clinical environment. To cope with the complex computational demands of huge biological datasets, a shift to distributed compute resources is unavoidable. A case study was conducted in which three well-established bioinformatics analysis groups across Australia were assigned to analyse exome sequence data from a range of patients with disorders of sex development. Initially these groups used their own in-house data processing pipelines producing results that were incomparable. Subsequently these groups used a common bioinformatics workbench based upon Galaxy and offered through the Australia-wide National eResearch Collaboration Tools and Resources (NeCTAR) Research Cloud. The results were improved however significant differences were identified. This paper describes the experiences in this work and the variability of results. We discuss the challenges in moving from bioinformatics research into supporting clinical diagnostics.

Diagnostic approaches of disorders of sex development (46, XY DSD) by genetic methods

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Background:

Disorders of sex developments (DSD) are identified as rare heterogenous groups of inherited and congenital disorders related to sex determination and differentiation. Translocation between chromosomes X and Y, which could result in SRY gene deletion, deletion in chromosomes 9p, 2q, 10q are some of the cytogenetic findings reported in 46, XY GD patients. Molecular defects are various types of mutations in genes involved in gonadal development such as SRY, DHH, SF1, DAX1 and WNT4. The genetic investigations comprised low-resolution analysis (karyotyping) to high-resolution approaches (array-based techniques) and molecular genetics techniques were carried out for detection of mutations in a few genes (SRY, NR5A1, DHH, androgen receptor (AR)) involved in sex development. Moreover, our effort was to have better insight for genetic managing of these patients. 37 Patients were investigated with cytomicolecular tests.

Result:

Samples with normal 46, XY karyotype were screened for mutations in some genes involved in DSD. Five patients (13.5% of all samples) showed deletion in SRY gene. Three patients were found to have heterozygote nucleotide change (c.82C>T) in 3'UTR region in exon7 of NR5A1 gene. All samples that showed no nucleotide changes in analyzed genes as well as patients with normal karyotype were further checked for more genetic abnormalities using MLPA technique. Our result confirmed deletions found in SRY by PCR. One deletion found in NR5A1 in one male patient. Moreover, duplication has been showed in the first exon of WN4 gene in three different patients. One patient had a deletion in 3q26.33. This deletion included the SOX2OT gene.

Conclusion:

Our studies show that except SRY, other candidate genes have a low ratio in the etiology of 46,XYDSD. Moreover, SOX2 gene could be added to the panel of DSD patient's analysis. However, since the etiology of patients with DSD is only known in 50% of cases, and regarding the various genetic heterogeneity, the use of high throughput techniques such as array and next generation sequencing are strongly recommended.

Molecular analysis of the AR gene in two patients with 46,XY CAIS - a recurrent (p.Agr616His) and a novel (p.Ile842Asn) mutations

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Androgen Insensitivity Syndrome (AIS) is one of the most common conditions in group of differences of sex development (DSD). The clinical phenotypes of AIS are variable and classified into three categories: complete (CAIS), partial (PAIS) and mild (MAIS) form, depending on the severity of androgen resistance. More than 800 mutations have been identified in Androgen Receptor (AR) gene. In most individuals with CAIS mutations were observed.

Here we present two cases of young females with 46,XY and typical phenotype of CAIS, referred to our team due to primary amenorrhea (aged 15 and 14, respectively). DNA was extracted from both patient and their mothers. A routine quantitative fluorescent PCR technique (QF-PCR) was used to prove rapidly the presence of SRY gene in the Y-chromosome. Molecular analysis of the AR gene (Xq11-12) was conducted using direct sequencing of the coding exons and intron-exonic borders. Sequencing analysis revealed missense mutations in both cases. Subsequently, a laparoscopic gonadectomy was performed in both cases.

In case 1 a mutation in exon 3 was detected, leading to p.Arg616His change located in DNA-binding domain (DBD) of the AR protein. The substitution was inherited from the heterozygous mother. Variant p.Agr6161His was previously reported in 9 females with CAIS, 2 males with ambiguous genitalia and PAIS and 1 male with MAIS.

Case 2 assessment demonstrated a novel substitution in exon 7 of the gene leading to p.Ile842Asn change. The mother was not a carrier and the mutation was de novo. On the same position a different substitution (p.Ile842Ser) was previously reported in female patient with ambiguous genitalia. Computational prediction of mutation effects categorized the discovered variant as probably damaging (score = 1.0).

In conclusion, finding genetic diagnosis in 46,XY CAIS cases could be helpful in clinical management of patients and binding phenotype-genotype correlations. Moreover, it has a great impact for genetic counseling strategy and particularly – for counseling the sisters of affected individuals when proband’s mother is a carrier.

P27 **Syndromic DSD; A study of 30 Egyptian cases using cytogenetic techniques.**

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Abstract:

Background: Sexual development is a complex process that involves many genes, pathways and interactions. Disorders of sex development (DSD) can result from a number of causes, some of which might cause an isolated disorder in the gonads while others may result in developmental syndromes “Syndromic DSD”; causes include gene defects, defects in biochemical pathways or unidentified causes. **Results:** over 3 years we collected 30 cases of “Syndromic DSD” and were studied by conventional karyotyping and FISH, selected cases had molecular testing done when it was feasible. Twelve cases showed chromosomal anomalies and 18 cases showed a normal karyotype; 4 of which were diagnosed clinically. **Conclusion:** Syndromic DSD should be addressed with a more global approach than isolated DSD, Cytogenetic techniques should be the first line of diagnosis and clinical judgment should direct molecular testing when needed. Correlation of the genotype to the phenotype of these complex cases is not always possible particularly in cases with chromosomal aberrations as the phenotype may vary based on the length of affected segment.

Phenotypic variability associated with NR5A1 gene mutations

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Background

Steroidogenic factor 1 (SF1) is a transcriptional regulator of genes involved in adrenal and gonadal development, steroidogenesis and reproduction. Mutations in *NR5A1* (encoding SF1) lead to disorders of sex development (DSD), mainly in 46XY individuals with normal adrenal function but also in those with isolated anorchia, variable hypospadias degree, adult male infertility or in 46XX individuals with primary ovarian insufficiency.

Patients and methods

Molecular analysis of the *NR5A1* gene was performed in five 46XY patients with a wide phenotypic spectrum and without evidence of adrenal insufficiency.

Results

Patient 1: 46XY girl diagnosed with complete gonadal dysgenesis, presenting primary amenorrhea and hypoplastic uterus. She carried in heterozygosis the novel p.Cys301Tyr (c.902G>A) alteration, located in exon 5 at the ligand-binding domain of the gene. Her asymptomatic mother presented the variation as a possible mosaicism. 'In silico' analysis with prediction software classified the variation as pathogenic.

Patient 2: 46XY girl harbouring primary amenorrhea, virilization, clitoral hypertrophy, hypoplastic uterus and without evidence of gonads. Mutational analysis revealed a novel heterozygous p.Glu304fs (c.910_913delGAGC) alteration, also in exon 5, presumably producing a truncated protein. Her asymptomatic mother presented the variation in heterozygosis.

Patient 3: A 46XY boy presenting with micropenis, scrotal hypospadias, bilateral cryptorchidism and bifid scrotum. He carried in heterozygosis the previously described p.His24Leu mutation.

Patient 4: A 46XY boy with micropenis and bilateral anorchia presented in heterozygosis the already reported disease-associated p.Gly146Ala polymorphism.

Patient 5: A 46XY boy presenting with scrotal hypospadias, unilateral cryptorchidism and bifid scrotum also presented in heterozygous state the p.Gly146Ala polymorphism.

Conclusions

Our findings support the already described complex phenotype expressivity, penetrance and variable inheritance pattern of *NR5A1* mutations, especially in heterozygosis, ranging from severe DSD phenotypes to completely asymptomatic carriers. Establishment of phenotype- genotype correlations remains unclear, and the search for modulating factors that could explain the spectrum of clinical manifestations continues. Nevertheless, genetic testing is important to confirm the differential diagnosis with other DSD, family counselling and also for improving management of patients and carriers.

Expression of Gonadoblastoma Y (GBY) locus in germ cells of gonads from DSD-XY female patients: risk assessment for occurrence of gonadoblastoma & dysgerminoma

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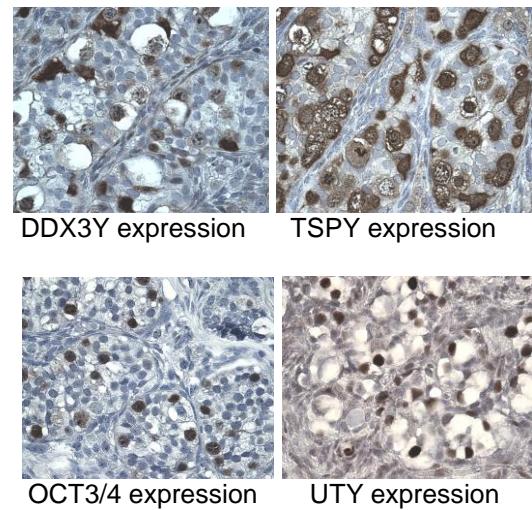
Background

Women with a Y chromosome in their karyotype (46,XY) are suffering from some disorder of gonad development (DSD-XY group). Clinically, these patients can display variable features of Turner syndrome (TS), partial/complete Androgen-Insensitivity-Syndrome (PAIS/CAIS) or the Swyer syndrome with usually streak gonads. Their germ cells seem to contain an inherent although variable risk (2-50%) to transform to pre-malignant gonadoblastoma cells which then can develop malignancy (dysgerminoma). It has been suggested that expression of the Gonadoblastoma-Y (GBY) locus, located on the human Y chromosome may be actively involved in this cellular oncogenic process. Indeed, immunohistochemical studies with antisera against TSPY –a protein encoded by one of the GBY genes (*TSPY*) - and OCT3/4 -well known as marker for presence of germ cell neoplasia- on gonadal tissue sections of DSD-XY individuals, displayed an overlapping expression pattern in gonadoblastoma cells. However, in males, *TSPY* like the other GBY genes, *DDX3Y* and *UTY* is also expressed in immature (fetal-like) germ cells. We therefore explored the expression pattern of these GBY genes now comparatively in immature and in gonadoblastoma germ cells observed in a series of gonadal tissue samples from patients with PAIS/CAIS or mixed or complete gonadal dysgenesis with 46,XY, or 46,XY/45,X0 karyotype.

Results

A clinical data base of 140 DSD-XY individuals has been established and bilateral gonadal tissue samples have been taken from 30 patients after written consent. Immunohistochemical analysis of *DDX3Y*, *TSPY*, *UTY* protein expression in the germ cells of these gonads revealed a comparable expression pattern for *DDX3Y* and *TSPY* in immature germ cells and in the pre-malignant gonadoblastoma cells mainly located in the undifferentiated part of the patients gonad tissue sections. *UTY* expression was only found in the germ cells nuclei. Most interestingly, it overlapped completely with expression of the germ cell specific OCT3/4 pluripotency marker (see Figure at the right).

When streak gonads which usually still contain some nests of undifferentiated germ cells, found in patients with Swyer syndrome, missed these germ cells, no expression of the GBY candidate genes, neither of OCT3/4 expression could be identified.



Conclusions

Data presented illustrate that the expression profile of the GBY locus in immature germ cells and in gonadoblastoma cells is comparable although often increased in the pre-malignant cell status, especially for *UTY*. This raises the question whether then only *UTY* is actively involved in the development of malignant germ cells in a dysgenetic female gonad tissue. It encodes a functional H3K27-Demethylase.

P30 Ovarian Adrenal Rest Tumour in a CAH patient

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Background

Ovarian adrenal rest tumours (OART) are very rare complications in female patients with Congenital Adrenal Hyperplasia (CAH). For the past 50 years, only ten cases of OART have been published worldwide. Ovarian adrenal rest tumours has been postulated to be caused by non-compliance with medication leading to excessive hormonal stimulation of adrenal rest tissues in ovarian tissue, which can also be due to undiagnosed CAH and Nelson's syndrome. This is a case report of this rare finding in a female patient with CAH in Malaysia.

Case

A 24 year old, diagnosed with CAH in infancy, with multiple co-morbidities and secondary amenorrhoea since age 15 years, presented with lower abdominal pain for a month. This patient has a confirmed learning disability and had undergone feminizing genitoplasty in childhood. She is known to have longstanding poor compliance to her steroids. For the past two years, she has had recurrent hospital admissions for various medical problems. Examination revealed an obese woman with stable vital signs and virilization features. Examination of her abdomen revealed abdominal striae with no mass palpable. Blood investigations showed elevated levels of serum testosterone, 17-OHP and plasma renin activity. Ultrasound scan of her pelvis showed bilateral solid ovarian cysts with no polycystic features. The patient refused to proceed halfway through the MRI procedure. Diagnostic laparoscopy revealed enlarged ovaries with a grayish appearance at the distal end of both ovaries. Frozen section of both ovarian biopsies were interpreted as ovarian adrenal rest tumours. Partial oophorectomies were then performed. Physically and psychologically, the patient was much improved post-surgery.

Conclusion

Ovarian adrenal rest tumours, even though extremely rare, need to be considered in women with CAH who have a long history of poor compliance to their medications and evidence of poor control such as virilization features. (294 words)

Long-term urinary symptoms in adolescent and adult women with congenital adrenal hyperplasia

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Background

Congenital adrenal hyperplasia(CAH) is an autosomal recessive condition resulting in excess androgen production. Females are typically born with ambiguous genitalia and often undergo feminizing genitoplasty. Recently, lower urinary tract symptoms(LUTS) have been reported as a common problem in these patients. Urinary symptoms can be grouped into one of three domains; filling, voiding or incontinence.

The aim of this study was to evaluate the prevalence of LUTS in a cohort of female CAH patients who have undergone feminising genitoplasty.

Methods

Females with CAH, aged 12-40 years, were identified from The Royal Children's Hospital databases.

Those aged 12-15 years were assessed using the Paediatric Incontinence Symptom Index questionnaire(ISI) in conjunction with sections of the Bristol Female Lower Urinary Tract Symptoms Scored Form questionnaire(BFLUTS-SF). Those aged 16-40 years were assessed using BFLUTS-SF. Uroflowmetry studies and post-void residual(PVR) volume ultrasounds were also conducted. Previously published normative data was used for the control population.

Results

43 women were invited to participate. Five declined and 23 completed one or more study components.

Three patients completed the ISI questionnaire, with one reporting symptoms of urinary incontinence. Responses to the BFLUTS-SF questionnaire indicated CAH patients had a higher incidence of urgency, frequency, urge incontinence, unexplained incontinence and nocturnal incontinence, when compared to previously published control data. Average and maximum urine flow rates measured by uroflowmetry were within normal range.

However the 16-40 year old age group did have a significantly increased mean PVR volume.

Conclusion

Overall CAH patients also appear to have normal urinary voiding function although increased PVR volumes. Preliminary data suggests that this population of CAH patients have an increased probability of incontinence, urgency, and frequency when compared to a control population. These results confirm findings of other small studies but it remains unclear if these changes reflect the underlying diagnosis or a consequence of management.

Managing genital difference in children with anesthesia risks: an alternative approach

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Background: Neurotoxicity concerns underlie 2014 pediatric anesthesia recommendations to defer non-essential procedures. The observed prevalence of neural changes in children with CAH merits cautious consideration of potentially neurotoxic interventions.

Findings: Animal studies provide compelling evidence of anesthetic neurotoxicity, with deficits in learning and cognition observed in children exposed to anesthesia before age 3.¹ The effect of surgery is known to be additive; 2014 international anesthesiology societies' expert recommendations include delaying non-essential procedures until after age 3.² Anesthetic neurotoxicity principally affects primates' hippocampus and temporal cortex,³ areas that may already be structurally and functionally altered in children with SWCAH.

European and US pediatric urology societies' stated goals of early genital surgery in children with DSD are: avoiding health hazards of atypical anatomy, meeting parents' expectations, and facilitating gender-concordant sexual function.⁴ Timing and appropriateness of genital surgery remain controversial; 50 years of surgical experience have not provided evidence of long-term physical or psychological benefit.⁵ Recent re-examination of data undermines claims that women prefer early surgery.⁶

Cognitive/psychological differences and structural brain changes are well described in SWCAH.^{7,8} For example, MRI studies of infants and children with SWCAH can show decreased volume/atrophy in the hippocampus, amygdala, temporal cortex, and corpus callosum; in addition, 45% of asymptomatic young adults with SWCAH had white matter changes on MRI, suggesting unexpected susceptibility to brain lesions.⁹ Furthermore, functional MRI of response to emotional stimuli in 46,XX SWCAH shows atypical activation patterns in the amygdala and hippocampus. These brain areas are also most susceptible to anesthetic neurotoxicity, raising concerns about potential additive effects of the neural and cognitive effects of SWCAH, and anesthetic exposure.^{10,11} Hormonal treatment to reduce infant genital difference, a potential alternative to surgery, shows promising results.^{12,13}

Conclusions: Because of potentially increased anesthesia risk for children with SWCAH, alternatives to surgery for managing family stress deserve consideration. Hormonal treatment, combined with prompt institution of psychosocial support, may facilitate development of coping and adaptation skills, allowing families to consider deferral of non-essential interventions, thereby reducing risks of adverse consequences, and allowing children to retain physical integrity until able to participate in shared decision-making.

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Pubertal Development in Individuals with Partial Androgen Insensitivity Syndrome (PAIS) Assigned Female Sex of Rearing

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Introduction

Data on long-term outcomes of girls with partial androgen insensitivity syndrome (PAIS) are scanty with no prospective studies detailing pubertal development. To begin to address this knowledge gap, the aim of this study was to evaluate pubertal development in patients with partial AIS (PAIS) assigned female sex of rearing.

Subjects and Methods

A cohort of individuals with the following criteria was identified through the International Disorders of Sex Development Registry (www.i-dsd.org) : 46,XY karyotype; female sex assignment; disorder of androgen action; PAIS; puberty data available; over the age of 16yrs. The search identified 20 girls from 10 centers in 6 countries; all center leaders were invited to participate in the study. This preliminary report of our ongoing study provides descriptive summaries of data from 7 of 20 cases for whom data have been provided.

Results

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Year of birth	1991	1995	1978	1993	1990	1991	1994
Approximate current age (years)	24	20	37	22	25	24	21
Original sex assignment	Female	Female	Female	Not provided	Female	Male	Female
Age at presentation (years)	1.0	1.2	1.0	Not provided	14.2	<0.1	11.0
Reason for presentation	Genital differences	Genital differences	Genital differences	Genital differences	Deep voice, hirsutism	Genital differences	Enlarged clitoris
AR mutation	Not found	I898T*	M895V*	S597G*	Not tested	Not tested	Not found
EMS at presentation	7.0	8.0	4.0	7.0	3.0	6.0	7.5
Age at genital surgery (years)	None	None	19.5	7.0	Not provided	1.5	10.5; 15.7
Genital surgery details	None	None	Clitoroplasty; creation of sigmoid neovagina	Clitoroplasty	Clitoroplasty	Clitoroplasty; vaginoplasty	Clitorectomy; ileovaginoplasty
Age at gonadectomy (years)	1.7	8.5	13.0	Not provided	14.8	5.0	11.5
Age at start of puberty (years)	9.4	11.3	10.0	12.8	Not known	10.7	Not provided
Age at completion of puberty (years)	14.0	14.1	15.5	15.3	Not known	13.2	18.2
<i>Findings at most recent review</i>							
EMS	3.0	0.0	0.0	Not provided	2.0	Unclear	0.0
Quigley scale	Not provided	5-6	5	5	5	6-7	6-7
Breast Tanner stage	B5	B5	B5	B4	B2	B5	B4
Pubic hair Tanner stage	P5	P3	P2	P4	P5	P5	P4-5
Axillary hair	Thick	None	None	Moderate	Thick	Thick	Not provided
Height (cm)	172	170	155	172	164	Not provided	Not provided
Type of estrogen therapy	Oral	Oral	Oral	Transdermal/Oral	Oral	Oral	Oral

Notes and abbreviations for table: all patients were prepubertal (Tanner stage 1) at presentation; AR = androgen receptor; EMS = external genital masculinization score (minimum = 0 [least male]; maximum = 12 [most male]); Quigley scale: 1 = fully masculinized external genitalia; 6-7=fully feminized external genitalia with (6) or without (7) pubic hair; not found = AR mutation testing performed and no mutation found; not tested = no AR mutation testing performed; *mutations have not been reported previously

It is notable that EMS was ≥6 for 5 girls, likely reflecting the prevailing practice of female sex of rearing in most cases of partial AIS in the 1990s. Age at onset of puberty was within the range of normal for all patients. Two girls without proven AR mutations and with intact testes underwent masculinizing changes at puberty.

Discussion

Additional data from PAIS girls and women with proven AR mutations, particularly those with testes retained through puberty, are needed to draw firm conclusions regarding pubertal development in girls with PAIS.

P34 **Management of gonads in adults with androgen insensitivity: an international survey**

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Introduction: Individuals with androgen insensitivity syndrome have an increased risk for the development of germ cell cancer (GCC). The risk is low during childhood; therefore, gonads are commonly preserved until after puberty. Little is known about GCC development in AIS during adulthood. This question becomes particularly relevant as many adult AIS women decline gonadectomy.

Methods: We conducted a questionnaire among health care professionals of DSD centers around the world, retrieved through the I-DSD Registry, assessing management of gonads in adult AIS individuals, reasons to decline gonadectomy and occurrence of GCC in gonads left in place.

Results: Response rate was low despite regular email invitations to participate in the survey. In complete AIS, gonadectomy is routinely proposed at the end of puberty in around 2/3 of centers, whereas in men with partial AIS, most but not all centers do not perform gonadectomy on a routine basis. Women who decline gonadectomy are anxious about surgery and complications. They also worry about long-term effects of lifelong hormone replacement therapy. Timing of surgery is sometimes not convenient, and should take into account processing of the diagnosis. Invasive GCC in gonads kept *in situ* were not reported by any of the respondents.

Conclusions: Regional differences in attitudes towards gonadectomy exist in centers caring for patients with androgen insensitivity syndrome. Individuals with AIS are concerned about surgery and hormone replacement therapy. On the other hand, the occurrence of an invasive GCC seems to be very rare in adults with AIS, questioning the necessity of performing gonadectomy in this population. Understanding the reasons why patients accept or decline gonadectomy, but also gaining further knowledge about GCC occurrence in adults with AIS specifically will help to improve counseling and patient-oriented management in the future.

PRENATAL DIAGNOSIS OF DSD: INITIAL EXPERIENCE OF A MULTIDISCIPLINARY TEAM

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Background: The improvement in quality of prenatal imaging and widespread genetic assessment has led to an increase of diagnoses of DSD conditions prenatally. A specialist multidisciplinary team (MDT) is crucial for clinical management and for providing support for parents/families from discovery of the suspected DSD through to birth and beyond. The aim of the current report is to present our initial experience.

Materials and methods: from March 2014 to February 2015, 4111 pregnancies have been followed in our Center. Thirteen (0,85 %) were found or referred from other Centers for suspected anomalies of the genitalia or DSD-related sex chromosome anomalies. During the same period three patients previously followed in our Center were found to have genital anomalies at birth that were not prenatally detected. Among 13 patients prenatally suspected for DSD, ten were subsequently defined as DSD conditions while 3 were eventually considered to have non-DSD related abnormalities. Postnatal assessment confirmed that 2 of the 3 non-DSD cases (buried penis initially referred as micropenis) were accurately labelled, with the remaining case presenting with proximal hypospadias at birth. The only case labelled as DSD in the prenatal period that was disconfirmed (not confirmed) at birth was a genital idiopathic edema in a 46XX fetus initially suspected for CAH.

Results: The accuracy (true positive rate) for prenatally suspected genital anomalies or variants by imaging or genetic analysis was 13/16 (81,25% sensitivity). Postnatal confirmation of cases initially referred for suspected DSD, but determined to be non DSD-related anomalies (true negatives) was 2/3 (66% specificity).

Discussion: Prenatal diagnosis of DSD may be considered a new frontier. Our impression is that parents in these cases have had more time to better assimilate complex informations as well as the opportunity to design a birth plan. The shock of a DSD diagnosis at birth may also be avoided (reduced). From the clinical management perspective, prenatal diagnosis may allow physicians to plan for medical treatment of morbidities associated with some DSD. However, our clinical impressions have not been empirically tested, and potential negative effects of a prenatal diagnosis must also be considered (the risk of false positives which may induce unnecessary anxiety). Further studies are needed to assess the true impact of this experience on patients and families involved in prenatal diagnosis of DSD.

Reason for referral	N	Prenatal suspicion/Postnatal diagnoses	
Genital ambiguity	10	4 - proximal hypospadias	all confirmed
		3 - buried penis	2 confirmed at birth, 1 hypospadias
		1 - 46,XX CAH	disconfirmed at birth
		2 - associated to other major malformations	confirmed at birth
Karyotype on amniocentesis/ villocentesis	3	1 - 45X,46XY with proximal hypospadias	confirmed
		1 - 45X,46XY with bilateral UDT	confirmed (one non palpable)
		1 - 45X,46XY with normal genitalia	confirmed

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Challenges in the management of affected children with different gender in a multiplex CAH family

Delayed referral: challenges in the clinical management of CAH in Indonesia

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Background: In late identified and untreated patients with 46,XX CAH, virilization come together with psychological and social consequences to patients and the family. We present a family that highlight these psychosocial aspects in the management of a family who raised four children with 46,XX CAH in the male and female gender.

Case presentation: The family consulted our team for the ambiguous physical appearance of the oldest girl, aged 18 (A). Seeking medical help was initiated by local government officer in the village. The family consisted of 10 children (4 dead in early life). Siblings were (B) a boy, 12 years, (C) a girl, 10 years, (D) a girl, 8 years, (E) a boy, 4 years and (F) a child with undecided gender of 2 years old. In four children (A,B,E,F) ambiguous genitalia were identified by the parents at birth whereas C and D showed normal physical examination. External genitalia of children raised male showed Prader stage > 3. The cytogenetic analysis of four children (A,B,E,F) revealed a 46,XX karyotype and hormonal analysis showed elevated 17OHP levels. Gender assignment was based on genital appearance, physical appearance, gender expression, and gender behavior in early years of life. The oldest girl and boy (A,B) reported emotional distress. Parents applied religious practice (frequently praying and seeking help from religious leader) in coping with problem. Patient B reported being outcasted because he preferred feminine-type activities. Diagnostic procedures and clinical management had been hampered by insufficient medical knowledge and knowledge of CAH, limited finance, and large distance from a medical expertise center.

Conclusions: Early clinical management of CAH may prevent many psychosocial problems. In many countries such care is not available, particularly not for poor people. Medications such as hydrocortisone and aldosterone are only available in capital city of Indonesia and not covered by government health insurance. It will be helpful for patients with CAH if government regulation enable hydrocortisone and aldosterone to be available at the primary care center or drug store or local hospital nearby.

P37 An anatomical hypospadias repair incorporating Y-V preputioplasty in distal urethral reconstruction

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Background The choice of the surgical technique in hypospadias surgery is largely based on the experience and skill of the operating surgeon, and subject to a qualitative assessment of the hypospadic urethra. According to the embryologically arrested development of the urethra, a hypospadias repair technique, in which ventral mobilization (Y-V plasty) of the foreskin in reconstruction of the distal urethra is described. The technique allows for the distal/glandular urethra to resemble the fossa navicularis, which is overlooked in distal urethral tubularisation.

Materials and methods Eighty six patients with (54 penile, 32 penoscrotal) hypospadias with variable degrees of chordee are operated with the described technique. Surgical technique: A Y-V plasty is performed on dorsal aspect of the abundant foreskin (forming hood or with so-called dog ears). A circumferential incision is completed between the proximal two arms of the Y incision. After degloving of the proximal (outer) and distal (inner) foreskin, ventral rotation of the distal foreskin is performed. It is reconstructed on the midline, as to cover the tubularised distal and glandular urethra, to form an anatomically correct, coronal-frenular collar. While, the glandular wings are approximated minimally on the midline, the ventral surface of the glandular urethra is covered by the diverted foreskin, in order to form a frenulum. Tubularized incised plate (TIP) repair with spongioplasty was carried out in all patients. The urethral stent was left open into the diaper for about 5 to 7 days.

Results At a mean follow up of 12 months, 2 (2 %) of the proximal hypospadias patients developed urethral fistula, 6 (7 %) patients had meatal stenosis, 2 with coronal meatus. Fistulas in both patients are repaired, patients with meatal stenosis/coronal meatus are cured with dilatation, successfully. All patients had cosmetically satisfying appearance, forty one with secondary circumcision.

Conclusion Ventral mobilization and reconstruction of the degloved dorsally hooded foreskin with Y-V plasty resulted with low complication rate and excellent postoperative results. It is observed that this method provided; 1- an anatomical restoration of the glandular urethra supported by a coronal-frenular collar, 2- a protective layer over the distal and glandular part of the tubularised neourethra with rich Dartos layer, and 3- the re-forming of the fossa navicularis.

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¹Clinical features in three patients with 46,XY DSD NR5A1 related

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⁸Background

⁹NR5A1 is nowadays considered one of the main genes causing 46,XY DSD. NR5A1 heterozygous
¹⁰mutations have de facto been found in 46,XY individuals with gonadal dysgenesis, as well as with a wide
¹¹spectrum of genital anomalies and, in some cases, with adrenal insufficiency. In 46,XX female deleterious
¹²variants in NR5A1 can be responsible of ovarian insufficiency. A specific clinical profile as well as
¹³natural history in individual 46,XY DSD patients with mutations in NR5A1 need to be further defined
¹⁴due to the relatively recent association of this gene to isolated forms of DSD.

¹⁵In order to give our contribute to identify specific characteristics, if any, shared between individuals with
¹⁶NR5A1 pathogenic variants, here we summarize the clinical findings in three patients seen at our
¹⁷Outpatients DSD's Clinic, who were found to be carriers of a mutation in this gene.

¹⁸Results

¹⁹The three individuals are part of a cohort of patients evaluated by us during childhood (one of these in the
²⁰neonatal period and the others from the second year of life) and successively followed throughout a
²¹variable period of time. Two patients had overt genital ambiguity at birth, while the third one was born
²²with predominantly female external genitalia and showed slight clitoral hypertrophy, not noticed during
²³the early neonatal period. Interestingly, in this girl, phallus length increased in the course of first year of
²⁴life. This patient, as well as another child who underwent gonadectomy in early life, were reared as
²⁵females. Gonads were located in the inguinal region in two patients (in the third one it was no possible to
²⁶know their position before surgery). While no uterus was identified in anyone, a huge vaginal pouch was
²⁷successively find in these subjects. Adrenal function was not altered. Testosterone levels, appeared to be
²⁸normal at birth and subsequently able to produce pubertal changes since the age of 12 in two of them not
²⁹underwent gonadectomy. De novo NR5A1 mutation was detected in all of them.

³⁰Conclusions

³¹The authors present the findings of three patients presenting at birth with genital ambiguity in whom a
³²specific aetiology was not identify and now reaching puberty. Later in life we re-evaluated this patients
³³and mutation of NR5A1 was found. SF1 (NR5A1) defect is often the aetiology of 46XY DSD
³⁴undiagnosed at birth, when the rule of this gene in testicular function and the following anomalous
³⁵development of genitalia was still largely unknown.

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Multi-disciplinary and Novel Approach to Treatment of 46, XY Disorder of Sex Development

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Background

The Gender & Sex Development Program at Lurie Children's Hospital is one of few joint gender development and disorder of sex development (DSD) programs in North America. A Mexican-born patient with ambiguous genitalia, now residing in the US, presented to our multidisciplinary program at age 8 years with limited evaluation and reared female. Parents were seeking diagnosis and management of the child's DSD.

Methods

Multidisciplinary assessment occurred across 7 visits over 29 months. Examination revealed small inguinal gonads, clitorophallic structure 3.5 cm, posteriorly fused labia with scant rugation, anterior perineal opening, long perineal body. Ultrasound demonstrated inguinal gonads, no Müllerian structures. Laboratory evaluation: Karyotype 46, XY, normal adrenal steroid intermediates, testosterone 1 ng/dL. HCG stimulation test: baseline testosterone 6 ng/dL, dihydrotestosterone < 5 ng/dL, post-stimulation testosterone 19.2 ng/dL, dihydrotestosterone < 5 ng/dL. *AR*, *5ARD2* and *LHCGR* gene analyses revealed no abnormalities. Endoscopy revealed a vaginal structure without a cervix. Left inguinal exploration confirmed structurally normal appearing testis and Wolffian structures. During psychosocial evaluation, the patient has consistently endorsed stereotypically feminine play and expressed female gender identity, but gender assessment has been limited by infrequent visits with the psychologist. At age 10 years, she entered puberty, with growth of the clitorophallic structure. Laboratory studies: LH 6.28 mIU/mL, FSH 15.6 mIU/mL, estradiol 2 pg/mL, testosterone 189.2 ng/dL, dihydrotestosterone 10 ng/dL.

Results

Assessment results suggest a 46, XY DSD of unknown etiology, likely a disorder of androgen synthesis or action. The multi-disciplinary team, having expressed concern to parents regarding the potential unwanted effects of pubertal virilization if the patient continues to identify as female, presented three treatment options: 1) no intervention 2) gonadectomy to permanently prevent further virilization, 3) GnRH agonist treatment for reversible pubertal suppression (PS). The recommendation for PS was informed by treatment of gender-variant youth in whom PS delays development of irreversible and undesired, peripubertal secondary sex characteristics. PS allows youth to cognitively mature so irreversible medical choices may be better made. Parents chose treatment with PS.

Conclusion

The approach to this patient illustrates the benefit of multidisciplinary collaboration in treatment of youth with DSD and potential gender concerns.

A tale of three Sudanese sisters with congenital adrenal hyperplasia

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Introduction: 21-hydroxylase deficiency is the most common cause of congenital adrenal hyperplasia (CAH). The condition can be divided into two major subtypes, the more severe salt-wasting (SW) variant and the simple virilizing (SV) variant. Mutations in the *CYP21A2* gene cause varying degrees of loss of 21-hydroxylase activity, resulting in different severities. Complete inactivation of 21-hydroxylase is associated with the SW phenotype, while those mutation that reduce enzyme activity to > 2% cause the SV phenotype. 46,XX fetuses with CAH are exposed to unusually high levels of androgens during fetal development, which variably masculinize the external genitalia and presumably also the brain and later have an impact on behavior. Several studies have shown that bisexuality and homosexuality are increased more in the SW than the SV variant or in CAH women with higher Prader stages of genital masculinization at birth.

In this study we are presenting three sisters with ambiguous genitalia. Molecular- genetic, steroids analysis and psychological assessment for gender identity problem were all investigated.

Results Their external genitalia showed variable degrees of masculinization. Cytogenetic analysis showed they have 46,XX karyotype. Their DNA was negative for *SRY* gene sequence. Steroids in urine were consistent with 21-OHD deficiency. *CYP21A2* gene analysis showed the homozygous mutation g.2872G>C (p.R483L). The psychological tests for cross-gender behavior showed that the two older sisters scored higher than the normal range, while the youngest sister scored within normal range.

Conclusion: The g.2872G>C (p.R483L) results in 1-2% of the enzyme residual activity invitro. This mutation is usually associated with simple virilizing form of CAH, which has no verification signs of salt losing. The high cross gender score in the two older sisters indicated they might have gender identity problem and this is could be due to the prolonged exposure to androgens. This is due to the influence of androgen on the brain effects female gender role in the 46,XX CAH individuals. This study shows the importance of the multi-disiplinary analysis for individuals with CAH which can help in understanding of each mutation and its effect on not only the phenotype but also on psychological development.

Development of a Decision-Making Checklist to Improve Care for Adolescents with Complete Androgen Insensitivity Syndrome (CAIS)

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Background:

Reports exist regarding the stepwise approach to the care of patients with differences or disorders of sexual development.¹ Each family has different values and styles of learning that have to be taken into account. The goals of care should include education about the condition, counseling of the patient and family, and a complete outlining of treatment options. It can be expected that this process will take multiple visits and should not be rushed.

Results:

We developed an organized checklist for providers to share with a patient and the family on the first visit. The development of the document enlisted input from physicians, social work, advocacy groups and affected individuals. It allows providers to explain the process of care and develop a plan for delivery of that care over multiple visits spanning six months or more. The checklist is divided into 5 sections: 1) an overview that addresses how much information is desired and in what manner the patient prefers to obtain information, 2) a preferred words list so that the patient can choose nomenclature that is most comfortable, 3) a list of topics that will be reviewed over the course of multiple visits, 4) a list of questions that a patient should have answered by the providers or other resources over time, and 5) a list of concerns that should be addressed before surgical intervention is considered.

Conclusions:

It is our hope that an organized approach to long-term delivery of compassionate care and accurate information can be accomplished for patients with CAIS by the use of a provider checklist. The documentation of this delivery of care can help guide referral to peer support for the patient and help ensure informed consent for treatment decisions. The use of the checklist should help facilitate trust in the provider and relieve stress for the patient and family. The checklist can be revised as new treatments and advanced technology emerges.

¹Foley, Sallie, and George W. Morley. 1992. Care and Counseling of the Patient with Vaginal Agenesis. *The Female Patient* 17 (October):73-80.

46XY ovotesticular DSD: what's the correct approach?

P42

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Background

Ovotesticular-DSD (OT-DSD) means the histological presence of both ovarian follicles and testicular elements in the same patient. OT-DSD is a very rare condition (about 1 in 45,000 births) and about 10% are 46XY. Gonadal tumors recur between 2.6 and 4.6% of OT-DSD. 46XY karyotype is more at risk. Malignant changes could occur in residual Mullerian tissue too. A rigorous follow-up is needed. Fertility potential preservation and a conservative approach is the goal in the treatment of DSD.

Case report

A newborn with genital ambiguity was transferred to our Institute: hypospadias without micropenis, severe penile curvature, no palpable gonads. No familiar, gestational or perinatal problems were reported. Fetal sonogram assessed a male phenotype. The after birth karyotype revealed a 46XY result. Cytogenetic analysis on peripheral blood excluded chromosomal mosaicism. Family social-economic status was low, parents strongly wanted a male gender assignment. Testosterone response after hCG stimulation was good. Abdominal sonogram and MRI showed uterine and vaginal structures confirmed through a diagnostic laparoscopy. On the left side a streak gonad was removed revealing, upon histologic examination, the presence of follicles; on the right side a vas deferens from the uterus was found and a testicle was biopsied confirming a regular male gonad. Orchiopexy and the first correction stage of the hypospadias were performed. Uterus, vagina and fallopian tube were not removed. The family received psychological support.

Conclusion

Conservative treatment is the goal in the multidisciplinary treatment of DSD, especially when the gender assignment is required during neonatal period. The choice should be done respecting:

- fertility potential
- concordant karyotype
- anatomical characteristics
- phenotype
- cultural and social conditions

Conserving the gonadal tissue appropriate with the sex of rearing is mandatory. None agreed guideline on the treatment of internal genitalia exists. We prefer to maintain Mullerian structures in a male patient. Gonadal and mullerian surveillance is then mandatory. Correction of external genitalia must guarantee the future possibility of a male to female genitoplasty

Herlyn-Werner-Wunderlich Syndrome with unusual presentation in a 15 years old girl

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Background: Herlyn-Werner-Wunderlich Syndrome is a rare combined anomaly of the Mullerian and mesonephric ducts characterized by uterus didelphys, obstructed hemivagina and ipsilateral renal agenesis. The incidence of this anomaly is reported to be between 0.1-3.8 %. It usually presents at puberty with pelvic pain during menstruation but may also present during adulthood with pelvic swelling or primary infertility. The treatment is surgical laparoscopic excision of the vaginal septum and successful pregnancy is achieved in 87 % of the patients. Endometriosis is a frequent complication of the syndrome that is why early diagnosis is beneficial.

Patient: We present a 15 years old girl admitted to our clinic because of arterial hypertension. She also had history of irregular menstrual cycle but without dysmenorrhea. On abdominal ultrasound the right kidney was not visualized but no other anomalies were noted. On abdominal CT scan agenesis of the right kidney was found with rudimentary hydroureter and ureterocele, two uteri with two separate cervixes and a cystic structure attached to the uteri. For the exact visualization of the anatomy of the internal genitalia MRI was performed revealing uterus didelphys bicornis, transversal vaginal septum, haematometrocolpos in the middle to distal third of the vagina and hydrocolpos in the proximal third. The patient was referred to a gynecologist for surgery.

Conclusions: Anomalies of the genital tract should be sought in patients with renal abnormalities as well as in girls with dysmenorrhea and irregular menstrual cycle. MRI is the method of choice for exact imaging of the genital anatomy. Early diagnosis and surgical treatment are important for the prevention of development of endometriosis and infertility.

Rare case of familial XY complete gonadal dysgenesis

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Individuals with 46,XY complete gonadal dysgenesis appear phenotypic female; however, they do not develop secondary sexual characteristics at puberty and are often diagnosed at adolescent age due to lack of menstruation. Bilateral 'streak gonads,' as well as a hypoplastic uterus and fallopian tubes are typical finding in the patients.

Herein, we report a Bulgarian family with a complete XY gonadal dysgenesis. Two sisters (21 and 18 years) with lacking pubertal development were referred for genetic testing. In both patients normal external female genitalia were observed. No clitoromegaly or labial fusion was described, and the vaginal introitus was normal. Pelvic examination revealed a hypoplastic anteverted uterus with no palpable gonads, ultrasound showed severely hypoplastic internal genitalia. The levels of gonadotropins in both women showed hypergonadotropic hypogonadism, while the levels of prolactin were in the reference ranges. No clinical signs of adrenal insufficiency were found. The karyotypes of both sisters were 46,XY and no chromosomal rearrangements were found at 400 GTG band level. Both were SRY positive by QF-PCR testing. Laparoscopic adnexitomy was performed in both because of increased risk for gonadoblastoma. Histological examination of gonads revealed fibrous ovarian cortical stroma without primordial follicles. The phenotype in patients corresponded to that of Swyer syndrome. Sequencing of SRY gene showed normal results. We assume that probably the siblings have inherited different maternal X chromosomes, as they present different alleles for three STR markers located in Xq13-q23. Despite this, X-linked form of XY gonadal dysgenesis due to duplication of NR0B1 gene could not be ruled out. There is no history for known consanguinity in the family but parents are from a small village and autosomal recessive form of XY gonadal dysgenesis is also possible.

P45 Complete androgen insensitivity syndrome – a case report and new trends in the management

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Background:

The most typical presentation of complete androgen insensitivity syndrome (CAIS) during infancy is inguinal hernia. Until recently simultaneous surgical repair of inguinal hernia and gonadectomy was a common practice. In the light of new findings gonadal preservation has become a widespread management.

Description:

A 10-day-old newborn was referred from the neonatal unit to the Department of Pediatric Endocrinology because of suspicion of a disorder of sex development. The baby was delivered at term with birth weight of 3250 g and Apgar score was 9. After birth oval swellings were visible in the inguinal regions. On ultrasound those structures were identified as testicles. On admission external female genitalia were visualised. Laboratory work-up revealed E2 11 [pg/ml], LH 0,44 [mIU/ml], FSH 0,2 [mIU/ml], cortisol 143 [ng/ml], ACTH 126,2 [pg/ml], TEST 1,46 [nmol/l], DHEA-S 11,82 [mcmol/l], ANDR 0,93 [ng/ml], 17-OHP 4,04 [ng/ml]. The result of karyotyping - 46,XY,inv(9)(p12q13). During next hospitalization, at the age of 31 days, bilateral inguinal hernias were present. The baby underwent a gynecological consultation - the vaginal length was 2,5-3 cm, the uterus was not visualised and a surgical consultation - bilateral reducible inguinal hernias containing both gonads. At that time hormone levels were as follows: LH<0,5 [mIU/ml], FSH [mIU/ml], TEST 0,69 [nmol/l]. Due to the lack of expected minipuberty the β hCG test (3x100j Pregnyl i.m.) was performed at the age of two months. The basal testosterone level rose from 0,27 [nmol/l] to 18,8 [nmol/l], and basal T/DHT ratio rose from 0,81 to 16,2. After clinical and biochemical confirmation of CAIS the decision was made to perform a surgical treatment of bilateral inguinal hernias with gonadal preservation.

Conclusions:

Because of poorly expressed mini puberty in infants with CAIS, β hCG stimulation test is often required in order to demonstrate proper testicular hormonal function. According to the new findings of low risk of gonadal tumorigenesis in CAIS and the possibility of spontaneous puberty in those patients, the decision of gonadal preservation during the surgical treatment of inguinal hernia becomes a common practice.

Newborns with Congenital Adrenal Hyperplasia and Markedly Virilized Genitalia: Considerations of Alternative Gender Assignments

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Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder of sex development (DSD) often leading to genital ambiguity. When the diagnosis of CAH is made in the first few months of life, it has traditionally been recommended that the gender of rearing, regardless of the degree of virilization of the genitalia, be female. The arguments favoring a female gender assignment are mainly centered around the preservation of fertility, because of the presence of potentially functional ovaries and uterus. In addition, this recommendation relies on outcome data that a female gender identity can be expected in the vast majority of the cases. However, recent data showed that gender dysphoria is experienced by approximately 5% of (assigned) girls with CAH, irrespective of the Prader stage of their genitalia at birth.

The purpose of this study was to analyze the decision making process of gender by the medical team and the family in a case of genetic female with markedly virilized CAH. The family was given both general information about CAH, and specific to the patient, including the genetic findings, showing mutations consistent with classic CAH, and endoscopy, showing a urogenital sinus with a high level of confluence and a bifid vagina. The parents were initially presented with the options of female and male gender assignment, elected to not choose any assignment, and to raise their child in a “neutral” gender. The interactions, between the members of the multidisciplinary clinical team (Urologist, Geneticist, Endocrinologist, Child Psychiatrist, Social Worker, Genetic Counselor) and between the clinicians and the family were tape recorded (after informed consent) and analyzed. The family has been followed up for over a year with recording and analysis of all interactions.

We review the factors to be considered for gender assignment, and discuss management strategies that promote the best possible quality of life across the lifespan for patients with CAH with markedly virilized genitalia.

A rare case of ovotesticular DSD associated with 46,XX/46,XY tetragametic chimerism.

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Background

Ovotesticular DSD (OTDSD), defined as the presence of both ovarian and testicular tissue, is an uncommon DSD diagnosis. Patients usually present with genital ambiguity at birth, and 46,XX is the most common karyotype. We present a rare case of an adult phenotypical male presenting to a local hospital with a painless right scrotal mass. Pathology of the gonadectomy specimen showed typical ovotestis. The patient was referred to our DSD center for further treatment.

Clinical information

Medical history was unremarkable, with the exception of gynecomastia since the onset of puberty at age 14 y. Physical examination showed a male phenotype with clear gynecomastia, normal masculine external genitalia, left scrotal gonad, and empty right hemi-scrotum after recent gonadectomy. His body showed several striking irregular pigmentations distributed, partially following the Blaschko lines. Initial ultrasound study of the left scrotal gonad showed homogeneous testis tissue. However, 6 weeks after presentation, he developed a cystic mass in the upper part of this gonad. Hormonal data, measured after right gonadectomy, were compatible with hypergonadotropic state with normal male level of T, low Inhibin B, high estrogen and prolactin. The karyotype in peripheral blood and buccal mucosa showed 2 cell lines: 46,XX and 46,XY. In both the testicular part of the ovotestis and the ovary part the XX and the XY cell lines were found, however in different proportions. Additional tests to differentiate between mosaicism of the sex chromosomes (46XX/47XXY/46XY) versus (tetragametic) chimerism were performed. Data and techniques are presented.

Results

Clinical and hormonal data on follow-up were compatible with the presence of a contralateral ovotestis, located in the scrotum. Tetragametic chimerism could be proven.

Conclusions

Chimerism can be a rare cause of OTDSD. Finding two different cell lines should lead to additional investigations to differentiate between mosaicism for the sex chromosomes or chimerism. Gynaecomastia persisting after puberty can in exceptional cases be the only clue to an underlying DSD. In contrast to the majority of OTDSD-cases, in which the genetic cause remains unsolved, the tetragametic chimerism in this man provides a full explanation for his phenotype.

The Disorders of Sex Development Translational Research network (DSD-TRN)

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The 2005 Chicago Consensus Conference identified areas for improvement in the clinical management of patients with DSD. In response, we undertook the creation of a multi-center clinical and research infrastructure dedicated to the discovery and dissemination of best practices in DSD healthcare. The DSD-TRN was launched in 2011 with the support of the US National Institutes of Health.

We hypothesized that optimizing health and quality of life outcomes for patients and their families requires:

- ❖ Reducing variability of practice across providers
- ❖ Commitment to investigation in practice areas where no consensus exists
- ❖ Use of gathered evidence to elaborate best practices
- ❖ Involvement of patient stakeholders in all activities of the network

The DSD-TRN provides methods and infrastructure to member sites, including:

- ❖ Standardized clinical forms for genetic, anatomy, endocrine and psychosocial assessment, customized for DSD diagnosis and management
- ❖ A registry to document current clinical practice and capture standardized, quantitative longitudinal data on the genetic basis of the condition, deep endocrine and anatomic phenotyping and psychosocial adaptation of patients and families
- ❖ Monthly clinical case videoconferences for all DSD-TRN member sites, attended by patient advocate representatives and an ethicist.

The DSD-TRN has now expanded from 4 to 10 interdisciplinary teams of clinicians and researchers who collaboratively develop a new standard of care, supported by research and the expertise of a robust and diverse Advisory Advocacy Network. Early deliverables include 18 novel clinical forms to document anatomy/surgery, endocrine and genetic practice, a comprehensive protocol for psychosocial assessment, a survey of current DSD clinical practices across the US, a proposed genetics-based protocol for accelerated path to accurate diagnosis, a registry with ~2000 unique documented traits, and a biobank.

Governing principles of the network, implementation so far, and remaining hurdles will be discussed. A major challenge remains the integration into clinical practice of new standardized protocols that impose change on clinician behavior, within the constraints of the US Health Care infrastructure. Resource constraints (e.g., clinician time, coordinating staff, limited availability of expertise – in particular behavioral health) represent systemic barriers that must be overcome to achieve truly comprehensive and integrated care in DSD.