Reproductive Endocrinology

TRANSGENDER, DSD, AND TURNER SYNDROME

Understanding, Communication and Concerns Around Sexual Development Differences by Patients' Perspectives

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Introduction: The approach to Differences of Sexual Development (DSD) patients is complex. It involves discussion on karyotype, gonads, genital phenotypes, hormonal treatment, genitoplasty, sexual activity and fertility. A satisfactory understanding by the patients optimize the follow up and the acceptance of the condition. **Objective/ Methods:** To analyze the understanding of DSD patients about their condition, the doubts and concerns, the barriers to communication and repercussion in gender, sexual orientation and relationships in a cohort of patients followed at a reference center, through a semi directed interview. **Results:** 57 patients were interviewed. The mean ages were 36.5y. Around 90% of all patients concluded at least the high school. Only 50% of all patients knew the condition's name and how they were affected by it. Still 92% knew the treatment. 63% of the patients presented doubts, mainly related to diagnosis. The median level of satisfaction about the condition understanding (on a scale from 1 to 5) was 4. Most of the patients were first informed by doctors (65%) or mothers (27%). The mean age of diagnostic disclosure was 13 y among patients with atypical genitalia. However, 67% of them preferred be first informed in childhood. Around communication, 60% of them reported no dialogue at home about the condition, 82% feel uncomfortable in talking to other people and 57% experienced negative comments related to DSD. Only four 46,XY DSD presented gender dysphoria: 3 with partial gonadal dysgenesis (who were admitted at the reference service after genitoplasty) and one 5-α-reductase 2 deficiency. About affective relationships, 42% of the patients were single and 70% had already experienced sexual activity. The mean age at first sexual activity was 22y. 72% considered that condition influences negatively on relationships because the stigma, the genitalia appearance, the insecurity in sexual intercourse and fertility. The concern related to stigma was higher among patients with atypical genitalia. The patients' self-evaluation (scale from 0 to 10) about their condition understanding improved after the interview: 6 to 8.9 ($p<0.01$). **Conclusion:** There is lack of knowledge about DSD among patients even treated in a referral center. The atypical genitalia arouses curiosity and stigma. Educational acts for patients, health team and community are needed to make DSD conditions popular, to improve the understanding and communication and to decrease the stigma.

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Understanding, Communication, Concerns and Repercussions of Sexual Development Differences by Mothers' Perspectives

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Introduction: Differences of sexual development (DSD) define congenital diseases in which an atypical development of chromosomal, gonadal or anatomical sex occurs. The approach involves complex themes: gender designation, genitoplasty, hormonal treatment and fertility. Mothers' understanding optimizes their children's assistance. Objective/methods: To analyze the mothers' understanding about the DSD condition, doubts, concerns, barriers to communication and repercussion in gender, sexual orientation and relationships in a cohort followed in reference centers in São Paulo (SP) and Ceará (CE), through an interview. **Results:** 112 mothers (72 from SP and 50 from CE) were interviewed. Mothers' mean age was 35 y. The satisfaction related to the understanding about their children's condition (on a scale from 1 to 5) was higher in the SP: medians of 4 (SP) and 3 (CE). Significant differences were evidenced between the numbers of mothers who knew the condition's name, 56.3% (SP) and 38.6% (CE); who knew why the children had been affected by it, 38.5% (SP) and 16.7% (CE); and who knew the drugs' function, 89.3% (SP) and 70.4% (CE). 70% to 83% of the mothers referred doubts, mainly related to the diagnosis and their feeling of guilt. Considering only children with atypical genitalia at birth (n:115), the difference was not diagnosed at hospital in 15% (4 from SP and 14 from CE). Pediatricians and obstetricians first communicated to mothers about the atypical genitalia in 73% of the reports. 70% (SP) and 41% (CE) of the mothers considered the first approach inappropriate. 89% of all mothers feel uncomfortable in talking to other people about the DSD condition and 68% experienced negative comments. Around 70% of mothers reported discomfort in exposing their children's genitalia and 64% considered genitoplasty as an urgency. 47% referred that the DSD may influence the gender identity, 65.4% referred it may prejudice relationships and 33.3% believed it may influence on sexual orientation. The concern related to stigma was higher than related to fertility, genitalia appearance, relationships, treatments, gender identity and sexuality. **Conclusion:** Most of the mothers of DSD children, even in reference centers, showed unsatisfaction and

lack of knowledge. The health team should be trained and the approach should consider the mothers' perspectives and be appropriate to the cultural context. Educational actions may improve understanding and reduce the DSD stigma.

Steroid Hormones and Receptors
STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Betamethasone Induces a Unique Transcriptome in Neural Stem Cells

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Twelve percent of pregnant women receive glucocorticoids (sGCs) to reduce the risks to reduce morbidity and mortality associated with preterm birth in infants. The two most commonly administered sGC are Dexamethasone (Dex) and Betamethasone (Beta) and they serve to decrease the severity of respiratory distress, intraventricular hemorrhage and necrotizing enterocolitis. However, repeated administration of sGC has been shown to be associated with adverse neurological outcome and depends on the type of sGCs used, dose, timing of sGCs administration and sex. We have previously shown that prenatal exposure to Dex in a murine model lead to sex specific changes in the transcription response and in the biological function of neural stem cells and to long-term changes in brain architecture and behavior. Beta is the predominant sGC used prenatally in the United States, therefore these studies investigated the cellular and molecular responses to beta exposure on the neural stem cells in-vitro and anatomical organization of the brain in-vivo. Murine NSCs were isolated from the E14.5 cerebral cortex and exposed to 10^{-7} M Dex, 10^{-7} M Beta, or Vehicle for 4 or 24 hours and the immediate and long-term impact on transcription, proliferation and neuronal, glial and oligodendrocyte differentiation examined. Affymetrix genome transcriptional analyses reveal sex specific responses to Dex vs Beta in 4 hours. In females 682 genes were differentially regulated by Dex compared to 576 by Beta. In contrast, 875 were altered by Dex and 576 by Beta in males (Fold change > +/- 1.5, P< 0.05). Select target genes were independently validated by QPCR. Ingenuity Pathway Analysis was used to identify unique and overlapping pathways that were altered by Dex vs Beta. In males, Dex uniquely altered 34 pathways including, Thyroid Hormone Metabolism, ERK5 Signaling and Opioid Signaling while Bata altered 33 pathways including, Phagasome formation, IL-7 Signaling and JAK STAT signaling. In Females, Dex altered 45 pathways including Calcium Signaling, Serotonin Receptor Signaling and Xenobiotic Signaling, while Beta altered 46 pathways including, FXR/RXR Activation, Tec Kinase Signaling and D-myo-Inositol-5-Phosphate Metabolism. Another 35 pathways were altered by both Dex and Beta but they showed differences in genes activated or repressed. Dex and Beta, both significantly altered genes involved in proliferation and differentiation therefore the biological response of NSC to sGCs stimulation in vitro and the long term consequences of sGC exposure in-vivo was compared. Distinct differences in cell proliferation, glial and oligodendrocyte differentiation were observed. These results reveal gene targets, cellular pathways and processes that are differentially altered by prenatal Dex vs Beta exposure. Our finds may provide insights into the sex specific neurological outcomes observed in children exposed to sGCs in-utero.

Steroid Hormones and Receptors
STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

A Novel Role of Nuclear and Membrane Receptor on Isoflavone-Induced Neuritogenesis and Synaptogenesis

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Thyroid hormone (TH) receptor (TR) and estrogen receptor (ER) play crucial roles in brain development. TR and ER are involved in dendrite growth, spines, and synapse formation in neurons. Soybean isoflavones, such as genistein, daidzein, and daidzein metabolite, S-equol are known to exert their action through TR, ER, and GPER1, a G-protein-coupled ER. However, the mechanisms of isoflavones action on brain development, especially during neuritogenesis and synaptogenesis, have not yet been extensively studied. We evaluated the effects of isoflavones using mouse primary cerebellar culture, astrocyte-enriched culture, Neuro-2A clonal cells, and co-culture with neurons and astrocytes. Soybean isoflavone augmented TH- or estradiol (E2)-mediated dendrite arborization of Purkinje cells. Such augmentation was suppressed by G15, a selective GPER1 antagonist, and ICI 182.780, an antagonist for ERs in both cultures. The knockdown of nuclear TRs or ERs also significantly reduced the dendrite arborization of Purkinje cells. It also increased the mRNA levels of TH-responsive genes, including *Mbp, Bdnf, Rc3, Ntf3*, *Camk2b, Hr*, and also *Syn1, Syp,* and *Psd95* that are involved in synaptic plasticity. Isoflavones also increased the protein levels of synapsin-1, synaptophysin, and PSD95 in dendrite and membrane fraction of the cerebellar culture. To study further the molecular mechanism, we used Neuro-2A clonal cells. Isoflavones also induced neurite growth of Neuro-2A. The knockdown of TRs, ERs, and GPR30 by RNAi reduced isoflavones-induced neurite growth. Moreover, the co-culture study of Neuro-2A and astrocytes also showed an increase in isoflavones-induces neurite growth. In addition, isoflavones increased the localization of synapsin-1 or synaptophysin and F-actin in filopodia tips during Neuro-2A differentiation. The knockdown of nuclear ERs or GPR30 significantly reduced the number of filopodia and synapsin-1 or synaptophysin expression levels in neurite and membrane fractions. However, there are no significant effects of