Controversies in the Management of Ambiguous Genitalia

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Session Summary

During this lecture the speaker will discuss the physiology of normal sexual differentiation, the pathophysiology of abnormal sexual differentiation, and the ethical issues involved in sex assignment in individuals with a disorder in sexual differentiation.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- understand the physiology of normal sexual differentiation;
- recognize the pathophysiology and clinical presentation of disorders of sexual differentiation;
- be sensitive to and be aware of the ethics of sex assignment in disorders of sexual differentiation.

References


Session Outline

See presentation handout on the following pages.
CONTROVERSIES IN THE MANAGEMENT OF AMBIGUOUS GENITALIA

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SEXUAL DIFFERENTIATION

• CHROMOSOMAL SEX
  – FEMALE- XX
  – MALE- XY

• GONADAL SEX
  – FEMALE- OVARIES
  – MALE- TESTICLES

• THE INTERNAL GENITAL DUCTS
  – FEMALE- FALLOPIAN TUBES, UTERUS, CERVIX, ANTERIOR 2/3’S OF THE VAGINA
  – MALE- VAS DEFERENS, EPIDIDYMUS, SEMINAL VESICLES

• THE EXTERNAL GENITALIA
  – FEMALE- VAGINA, CLITORIS
  – MALE- SCROTUM, PENIS

ETHICAL CONSIDERATIONS IN THE MANAGEMENT OF THE PATIENT WITH INTERSEX

TOPICS TO BE COVERED

• SCIENTIFIC BACKGROUND

• JOHN MONEY AND “THE STANDARD MODEL”

• THE DEMISE OF THE STANDARD MODEL

• CURRENT CONTROVERSIES

SEXUAL DIFFERENTIATION

• THE UNION OF TWO Xs LEADS TO A 46, XX OR FEMALE KARYOTYPE

• THE UNION OF AN X WITH A Y LEADS TO A 46, XY OR MALE KARYOTYPE
GONADAL DETERMINATION

EMBRYOLOGY

- In 46, XX individuals, the gonads become ovaries.
- In 46, XY individuals, the gonads become testicles.

THE INTERNAL GENITAL DUCTS

- Early in gestation, all fetuses have both male and female genital ducts.
- The female genital ducts are the Müllerian structures.
- The male genital ducts are the Wolffian structures.

THE INTERNAL GENITAL DUCTS

MALE

- The male internal genital ducts are known as the Wolffian ducts.
  - Vas deferens
  - Seminal vesicles
  - Epididymis

- If the gonad is a testis:
  - Testicular cells produce a substance (MIS) that causes involution of the Müllerian ducts.
  - Testicular cells also produce testosterone, which allows the Wolffian ducts to develop.

FEMALE

- The female internal genital ducts are known as the Müllerian ducts.
  - Fallopian tubes
  - Uterus
  - Cervix
  - Anterior 2/3's of the vagina

- If the gonad is an ovary:
  - No MIS is produced.
  - The Müllerian structures develop.
  - No testosterone is produced.
  - The Wolffian structures regress.

DIFFERENTIATION OF THE EXTERNAL GENITALIA

MALE

- The external genitalia of the early gestation fetus are undifferentiated and bipotential.
- Differentiation of the external genitalia into a scrotum and a penis requires intense androgen stimulation early in fetal life.
  - Testicular cells produce testosterone, which is converted to dihydrotestosterone by 5-alpha-reductase.
  - Dihydrotestosterone is crucial in the virilization of the external genitalia.
  - Closure of the vaginal opening only occurs with dihydrotestosterone.

FEMALE

- In the absence of androgen, the external genitalia will differentiate into a clitoris and a vagina.
DISORDERS OF SEXUAL DIFFERENTIATION

THE FIRST REPORTED CASE OF 5-ALPHA REDUCTASE DEFICIENCY

“MUCIANOS INFORMS US THAT HE ONCE SAW AT ARGOS A PERSON WHOSE NAME WAS ARESCON BUT HAD FORMERLY BEEN ARESCUSA. THAT THIS PERSON HAD BEEN MARRIED TO A MAN BUT THAT SHORTLY AFTERWARD HE DEVELOPED A BEARD AND OTHER MALE CHARACTERISTICS, UPON WHICH HE TOOK A WIFE.”

PLINY THE ELDER, HISTORIA NATURALIS, 77 ACE

DISORDERS OF SEXUAL DIFFERENTIATION

MALE UNDERRIRILIZATION

5 ALPHA REDUCTASE DEFICIENCY

• 5-ALPHA REDUCTASE DEFICIENCY IS CHARACTERIZED BY UNDERPRODUCTION OF DIOHIDROTESTOSTERONE
  • THIS LEADS TO POOR PHALLIC GROWTH AND INCOMPLETE CLOSURE OF THE UROGENITAL SINUS. DURING PUBERTY THE PHALLUS ENLARGES BUT THE UROGENITAL SINUS REMAINS OPEN
  • THERE IS A GROUP OF VILLAGES IN THE DOMINICAN REPUBLIC WHERE INDIVIDUALS WITH THIS CONDITION ARE RAISED AS FEMALES DURING CHILHOOD AND SWITCHED TO MALES AT ADOLESCENCE

DISORDERS OF SEXUAL DIFFERENTIATION

ANDROGEN INSensitivity SYNDROME

• THE CHROMOSOMES ARE 46, XY SO THE GONADS DIFFERENTIATE INTO TESTICLES
  • TESTICULAR CELLS MAKE MUS TO THE MULLERIAN STRUCTURES REGRESS
  • TESTICULAR CELLS ALSO MAKE TESTOSTERONE BUT THE BODY CAN’T “SEE” IT
  • THE WOLFFIAN STRUCTURES REGRESS
  • THE PHALLUS REMAINS SMALL
  • THE VAGINAL OPENING DOES NOT CLOSE

DISORDERS OF SEXUAL DIFFERENTIATION

EXCESSIVE FEMALE VIRILIZATION

CAUSES

• MATERNAL INGESTION OF ANDROGEN DURING GESTATION
  – MEDROXYPROGESTERONE, ETC.

• EXCESSIVE PRODUCTION OF ANDROGEN BY THE FETUS
  – CAH, ETC.

DISORDERS OF SEXUAL DIFFERENTIATION

EXCESSIVE FEMALE VIRILIZATION

EXCESSIVE VIRILIZATION

VIRILIZING ADRENAL HYPERPLASIA

• THE CHROMOSOMES ARE 46, XX SO THE GONADS DIFFERENTIATE INTO OVARRIES
  • OVARRIES MAKE NO MUS TO THE MULLERIAN STRUCTURES PERIST
  • THE OVARRIES MAKE TESTOSTERONE
  • THE PHALLUS IS ENLARGED
  • THE VAGINAL OPENING UNDERGOES PARTIAL/COMPLETE CLOSURE
DISORDERS OF SEXUAL DIFFERENTIATION

HERMAPHRODITES

• TRUE HERMAPHRODITES HAVE BOTH OVARIAN AND TESTICULAR TISSUE
  – OVARIES
  – TESTES
  – INTERNAL GENITAL DUCTS DIFFERENTIATE ACCORDING TO THE AMOUNT OF ANDROGEN
  – OVARY ON ONE SIDE, TESTICLE ON THE OTHER
  – MULLERIAN STRUCTURES DEVELOP ON THE OVARIAN SIDE
  – WOLFFIAN STRUCTURES DEVELOP ON THE TESTICULAR SIDE
• THE EXTERNAL GENITALIA DIFFERENTIATE ACCORDING TO THE AMOUNT OF ANDROGEN

THE ETHICS OF INTERSEX

FROM THE 1950S TO THE 1990S

PHYSICIANS APPROACHED INTERSEX PATIENTS USING A MODEL DEVELOPED BY DR. JOHN MONEY AND ENDORSED BY DR. LAWSON WILKINS

THE ETHICS OF INTERSEX

JOHN MONEY WAS A PSYCHIATRIST AT JOHNS HOPKINS MEDICAL SCHOOL

– HE PROPOSED THAT MALES AND FEMALES HAD THE SAME BRAIN BIOLOGY. AS A CONSEQUENCE, THERE WERE NO STRICTLY MALE OR FEMALE BEHAVIORS, ONLY LEARNED BEHAVIORS
– HE WAS CONSIDERED VERY PROGRESSIVE IN THE 1950S

THE ETHICS OF INTERSEX

LAWSON WILKINS WAS A PEDIATRICIAN AT JOHNS HOPKINS WHO FOUNDED THE FIELD OF PEDIATRIC ENDOCRINOLOGY

ALL PEDIATRIC ENDOCRINOLOGISTS ARE “DESCENDED” FROM LAWSON WILKINS

– HE AND HIS IMMEDIATE DISCIPLES HELD TREMENDOUS SWAY IN THE FIELD OF PEDIATRIC ENDOCRINOLOGY
– HE COLLABORATED WITH JOHN MONEY IN FORMULATING WHAT CAME TO BE CALLED “THE STANDARD MODEL” OF MANAGING INTERSEXED PATIENTS

THE ETHICS OF INTERSEX

CHILDREN WITH INTERSEX

THE STANDARD MODEL

• CHILDREN WITH INTERSEX MUST HAVE NO DOUBTS ABOUT THEIR GENDER IDENTITY.
• PARENTS, AS THE PRIMARY PROVIDERS OF THE INTERSEXED CHILD’S SOCIOCULTURAL ENVIRONMENT, MUST HAVE NO DOUBTS ABOUT THEIR CHILD’S GENDER IDENTITY.
• TO ASSURE THAT THERE IS NO AMBIGUITY IN THE PARENTS’ OR THE CHILD’S MIND ABOUT THE INTERSEXED CHILD’S GENDER IDENTITY, PHYSICIANS MAY USE SUBTERFUGE TO DISGUISE THE EXTENT OF THE PATIENT’S AMBIGUITY
THE STANDARD MODEL

• FOR FORTY YEARS ALL PEDIATRIC ENDOCRINOLOGISTS WERE TAUGHT THE STANDARD MODEL AND APPLIED IT TO THEIR PATIENTS WITH INTERSEX

ANDROGEN INSENSITIVITY SYNDROME

• THE GENOTYPE IS 46, XY (SRY POSITIVE) SO THE GONADS DIFFERENTIATE INTO TESTICLES

• TESTICULAR SEROTI CELLS MAKE MULLERIAN STRUCTURES REGRESS

• TESTICULAR LEYDIG CELLS MAKE TESTOSTERONE BUT THE BODY CAN'T "SEE" IT

• THE PHALLUS REMAINS SMALL

• THE VAGINAL OPENING DOES NOT CLOSE

THE STANDARD MODEL

TYPICAL EXAMPLE

• AIS PATIENTS AND THEIR PARENTS WERE TOLD
  – YOUR DAUGHTER IS XX BUT A PIECE OF ONE OF THE Xs BROKE OFF
  – YOUR DAUGHTER'S OVARIES DID NOT DEVELOP PROPERLY AND NEED TO BE REMOVED

THE STANDARD MODEL

UNDER FIRE

• IN THE 1990s SOCIAL SCIENTISTS BECAME INTERESTED IN THE INTERSEXED AS A WINDOW ON GENDER ROLES AND GENDER IDENTITY

• THEY “DISCOVERED” THE STANDARD MODEL AND WERE APPALLED

THE STANDARD MODEL

UNDER FIRE

• ALMOST SIMULTANEOUSLY SOME PEDIATRIC ENDOCRINOLOGISTS STARTED TO QUESTION THE STANDARD MODEL

• MY PERSONAL JOURNEY
  - I WITNESSED AN INCIDENT IN WHICH A 20 YEAR OLD AIS PATIENT CONFRONTED ONE OF MY COLLEAGUES IN PUBLIC AND ACCUSED HIM OF LYING TO HER

• IN THE 1990s I WAS IN THE MEDICAL ETHICS PROGRAM AT THE UNIVERSITY OF CHICAGO. IT DID NOT TAKE ME LONG TO REALIZE THAT THE STANDARD MODEL VIOLATED EVERYTHING I WAS BEING TAUGHT

• I, ALONG WITH A SMALL NUMBER OF COLLEAGUES, STARTED TO SPEAK OUT AGAINST THE STANDARD MODEL

THE STANDARD MODEL

THERE IS A BIG PROBLEM WITH THE STANDARD MODEL:

IT IS WRONG:

ETHICALLY

SCIENTIFICALLY
THE STANDARD MODEL
ETHICAL CRITIQUE

WHEN I ASKED MY COLLEAGUE JOEL FRADER, A PEDIATRICIAN AND ETHICIST AT NORTHWESTERN MEDICAL SCHOOL WHICH ETHICAL PRINCIPLES THE STANDARD MODEL VIOLATED, HE SUCCINCTLY REPLIED:

“ALL OF THEM”

THE STANDARD MODEL
CRITIQUE FROM PATIENTS

PATIENTS EVENTUALLY FIND OUT THE TRUTH ABOUT THEIR DIAGNOSIS AND STRONGLY RESENT HAVING BEEN LIED TO.

LYING AND SUBTERFUGE ARE INEFFECTIVE AND DESTRUCTIVE BECAUSE PATIENTS ALWAYS KNOW SOMETHING IS “WRONG” WITH THEM.

THE STANDARD MODEL
SCIENTIFIC CRITIQUE

THE CASE OF BABY M

BABY M WAS A NORMAL MALE INFANT WHO LOST HIS PENIS AT 7 MONTHS OF AGE FROM AN ERROR MADE DURING HIS CIRCUMCISION.

HE WAS TAKEN TO DR. MONEY WHO RECOMMENDED CASTRATION AND SEX REVERSAL.

FOLLOW UP PSYCHOLOGICAL EVALUATIONS AT YEARLY INTERVALS INDICATED THAT BABY M HAD TRANSITIONED SMOOTHLY TO THE FEMALE GENDER.

AT 15 YEARS OF AGE THE PATIENT STATED HE WAS “MALE” AND ADOPTED A MALE GENDER ROLE.

THE STANDARD MODEL
SCIENTIFIC CRITIQUE

CAH IN 46,XX INDIVIDUALS

STUDIES PRIOR TO 1998 SUGGESTED THAT 46,XX INDIVIDUALS WITH CAH HAD FEMALE GENDER IDENTITIES WITH A SOMEWHAT INCREASED INCIDENCE OF LESBIANISM.

AFTER 1998 A NUMBER OF STUDIES INDICATED THAT THE INCIDENCE OF GENDER DYSPHORIA WAS 3-5% AND OF LESBIANISM IN THE 10-20% RANGE.

ISNA NUMBERS INDICATE GENDER DYSPHORIA IN 5-10% AND LESBIANISM IN 50-50%.

THE STANDARD MODEL
SCIENTIFIC CRITIQUE

THE CUBAN EXPERIENCE

ALL PATIENTS WITH CAH IDENTIFIED IN CUBA ARE REFERRED TO THE NATIONAL INSTITUTE OF ENDOCRINOLOGY.

THESE PATIENTS UNDERGO EXTENSIVE PSYCHOLOGICAL TESTING.

33% OF THE 46,XX INDIVIDUAL HAD MALE GENDER IDENTITIES. THERE WAS ONE LESBIAN.

MANAGEMENT OF THE CHILD WITH INTERSEX

BASED ON THESE AND OTHER STUDIES IT IS BECOMING CLEAR THAT GENDER IDENTITY IN INTERSEXED PATIENTS IS HIGHLY UNPREDICTABLE EARLY ON.

INTERVENTIONS DESIGNED TO COSMETICALLY ESTABLISH A MALE OR FEMALE SEX RUN A SIGNIFICANT RISK OF DISCORDANCE WITH THE PATIENTS EVENTUAL GENDER IDENTITY.
MANAGEMENT OF THE CHILD WITH INTERSEX

THE "NO INTERVENTION" MODEL PROPOSED BY INTERSEX ACTIVISTS AND MANY ETHICISTS

- INTERSEX ACTIVISTS PROPOSE THAT, UNLESS MEDICALLY INDICATED, THE GENITALIA OF INTERSEXED CHILDREN SHOULD NOT BE ALTERED.
- WHEN THESE CHILDREN REACH THE AGE OF CONSENT THEY WOULD CHOOSE WHETHER TO HAVE SURGERY ON THEIR GENITALS.

THE NO INTERVENTION MODEL WORST CASE SCENARIO

- THE NO INTERVENTION MODEL FAILS TO ADDRESS EXTREME SITUATIONS SUCH AS THE FEMALE WITH CAH WHO IS COMPLETELY VIRILIZED – THE CHROMOSOMES ARE 46,XX – THERE ARE WORKING OVARES AND A UTERUS – THE PATIENT WOULD BE FERTILE AS A FEMALE, BUT INFERtile AS A MALE.
- THE GREAT MAJORITY OF PARENTS WHO TO RAISE THE CHILD AS A FEMALE AND WANT RECONSTRUCTIVE SURGERY IMMEDIATELY SO THAT THE CHILD'S APPEARANCE MATCHES THE GENDER OF REARING.

MANAGEMENT OF THE CHILD WITH INTERSEX

A MIDDLE WAY

- THE "HOPKINS" MODEL IS LEGALLY AND ETHICALLY UNTENABLE.
- THE MODEL PROPOSED BY INTERSEX ACTIVISTS IS NOT PRACTICAL OR REALISTIC. IT ALSO IGNORES THE DECISION MAKING ROLE OF THE PARENTS.

MANAGEMENT OF THE CHILD WITH INTERSEX

A MIDDLE WAY

- WE PROPOSED A MODEL IN WHICH PARENTS OF INTERSEXED CHILDREN ARE FULLY INFORMED OF THEIR CHILD'S CONDITION.
- THE PARENTS WOULD THEN DECIDE THEIR CHILD'S GENDER ASSIGNMENT AND NEED FOR SURGICAL INTERVENTION.

MANAGEMENT OF THE CHILD WITH INTERSEX

CURRENT PRACTICE

- MOST PHYSICIANS INVOLVED IN THE CARE OF THE INTERSEXED PATIENT PRACTICE SOME FORM OF THE MIDDLE WAY
  - THEY FULLY INFORM THE PATIENT/PARENT OF THE CONDITION
  - IF THE PATIENT IS AN INFANT, THEY FOLLOW THE PARENTS WISHES WITH RESPECT TO GENDER OF REARING AND SURGERY
  - THE OLDER THE CHILD, THE MORE THE CHILD'S PREFERENCES ARE TAKEN INTO ACCOUNT

MANAGEMENT OF THE CHILD WITH INTERSEX

CURRENT PRACTICE- CONTROVERSIES

- MOST INTERSEX ACTIVISTS AND ETHICISTS REJECT A "MIDDLE WAY" ESPECIALLY IN CASES WHERE THE SURGERY IS COSMETIC – CLITORAL REDUCTION
- PARENTS ARE EQUALLY ADAMANT THAT THEY HAVE THE RIGHT TO CHOOSE SURGERY IN THESE CASES.
MANAGEMENT OF THE CHILD WITH INTERSEX

CONCLUSION

• I BELIEVE THAT SOCIETAL ATTITUDES WILL EvOLVE SO THAT SURGERY WILL ONLY BE PERFORMED IN THE MOST EXTREME CASES OF ANATOMICAL DISSONANCE

• AN OPEN AND RESPECTFUL DIALOGUE BETWEEN INTERSEX ACTIVISTS, ETHICISTS AND THE PHYSICIANS INVOLVED IN THE CARE OF INTERSEXED PATIENTS IS CRUCIAL IN SECURING A POSITIVE PHYSICAL AND EMOTIONAL OUTCOME FOR THESE CHILDREN

HERMES + APHRODITE = HERMAPHRODITUS

“SINGLE FORM, POSSESSED OF A DUAL NATURE, WHICH CANNOT BE CALLED MALE OR FEMALE, BUT SEEMED TO BE AT ONCE BOTH AND NEITHER. THE MOST PERFECT OF THE GODS, HAVING BOTH MALE AND FEMALE ATTRIBUTES”

OVID, 3RD CENTURY B.C.E.