Gender assignment for patients with intersex is an essential but very delicate issue. In Asia, each country has a different culture and may approach gender assignment differently. Historically, male assignment had been valued because the male was considered physically superior to the female in the labor force, and the head of family was always male and he strongly hoped to have a baby boy as an heir. On the contrary, for many years, most surgeons believed that female genitoplasty was easier than male genital reconstruction. It meant that surgery to reduce clitoral size or to remove the clitoris was easier than building a phallus. However modern pediatric urologic surgery has made it possible to create equally female genitalia or male genitalia cosmetically and functionally.

Although many obstetricians and neonatologists may be influenced by the appearance of external genitalia in gender assignment even now, it is noteworthy that in these papers from four different countries, gender assignment is made by a multidisciplinary approach. Each author discusses various aspects, not only surgical capability but genetic and endocrine issues. Even though we have made such progress, the gender assignment is still complicated in some cases and if a census registration system is adopted as in Japan, they have to determine the sex within the time limit. Nevertheless, we must be very careful to decide the gender assignment because if the sex is not appropriate for the patient during his or her growing years, we have to convert his or her gender. While it may be possible surgically, it is a very complicated process socially and legally.

These four papers were presented in a symposium entitled “Intersex: Sex Assignment in Asia” at the 7th Annual Meeting of the Asia Pacific Association of Pediatric Urologists, held in Kyoto, Japan in October, 2005.

Sex assignment in cases in newborns with a disorder of sexual development continues to be a challenge. In the past our goal had been to normalize to a male or female sex, taking into consideration genital reconstructability and fertility potential primarily. It is quite clear today that the phenotypic appearance of a child before or after reconstruction and the fertility potential may have little to do with one’s gender identity. Most of what has been written on this subject of late has paid little attention to cultural differences in particular societies that may drive sexual assignment. This issue of the Dialogues looks at such cultural issues in Asia from four different countries. Dr. Tanikaze has put together an excellent group of contributors, all with significant experience in their own culture with this problem. What one comes away with is that for all of the physiologic and pathophysiologic information that we have to date; there are clearly other psychosocial factors which may be individual to certain societies that influence decisions in this field. Dr. Reiner provides a special commentary on issues related to sexual assignment for disorders of sex development and in that commentary emphasizes a need for a multidisciplinary approach.

I commend Dr. Tanikaze and his contributors for an excellent issue that provides us with more food for thought on this complex topic.
Gender identity is a central attribute of being human. It represents one of the three primary components of psychosexual development, the others being sex typical behaviors and sexual orientation. Sex assignment of a newborn, therefore, dictates a potentially profound social and clinical course. Problems of sex assignment may occur when a newborn has a disorder of sex development (DSD). Errors of sex assignment in cases of DSD may lead to gender dissatisfaction, atypical sex behaviors—not “fitting in” with same-sex peers—and apparently homosexual erotic orientation. Additionally, and perhaps most important, a neonatal sex assignment error may lead to subsequent self-reassignment in childhood, adolescence, or even adulthood. Thus, sex of rearing is not an attribute to be assigned lightly in such children. The articles in this issue describe both the clinical approaches for sex assignment of a newborn with anomalous genitalia within a number of Asian countries and the changing medical-clinical climate of making determinations of sex assignment at birth. Of particular interest are the culture-specific gender-related attitudes expressed here, simultaneously with the recognition that varying and changing decision-making algorithms for determining sex assignment exist not only across these cultures but even within each specific culture itself. This speaks to the growing scientific recognition that we do not have very many answers for clinicians. We have, yet, too few questions.

Neonatal genital anomalies present broad psychosexual developmental uncertainties. Clinical outcomes studies are few. However, those few studies relate unpredictability of gender identity outcome in terms of sex assignment in infancy. This reality stands in the face of some fairly clear data on prenatal androgen exposure and its effects. Indeed, there are androgen exposure dose-related effects on behavior and toy choice in genetic females with CAH—those with more severe mutations and marked genital virilization have more male typical behaviors than the others. This seems to coincide with studies of genetic males exposed to typical amounts of androgen in utero, such as those with cloacal extrophy, and may coincide with studies of those with micropenis as well. Effective prenatal androgen exposure can also be associated with other psychosexual developmental characteristics such as sexual orientation and nurturing or maternal interests. Additionally, androgens both affect and effect aspects of sexual dimorphism of brain development, and specific sex chromosome effects have been recognized in a number of species as well; some of these effects have been recognized in humans. However, cause-and-effect relationships are poorly understood—relationship to phenotype, therefore, is poorly understood.

Because of the prevalence of such distinct and clinically important unpredictability in gender outcome and gender identity etiology—often apparently independent of diagnosis, androgen exposure, sex-rearing, or other social and biological factors—sex assignment of a newborn with anomalous genitalia is today a more ethnically and clinically demanding decision-making process than ever before. There is no standard of care that applies to all patients with any given DSD diagnosis except, perhaps, complete androgen insensitivity (46,XY neonates should be reared female) and vaginal (Mulherian) agenesis syndrome (46,XX neonates should be reared female). Genetic females with congenital adrenal hyperplasia are almost always—but not always—reared female and greater than 90% (but not all) identify as female. Genetic males with micropenis should probably be reared male, and strong consideration should be given to rearing as male those neonates who are 46,XY but born with a severely inadequate or absent penis but normal testes and normal androgen receptors—these children will have male-typical gender behaviors, most likely will have sexual orientation towards (sexual interest in) females, and many or most of these children will be potentially fertile with fertility-assistance techniques; they are likely to adapt to male sex-assignment much like those with micropenis. It is critical, therefore, that multidisciplinary teams be established for the specific purpose of evaluating the child with a DSD and the parents, advising the parents and the primary care physicians, and managing and continuing to advise the child with DSD and the parents lifelong, or as necessary.

Unfortunately, such complete teams are few in the Americas and Europe. Those that do exist appear to function only occasionally as a team, with unclear individual and group responsibilities and with excessive fluidity of membership. Perhaps the Asian medical communities can assist all of us—and thus all of these children—by blazing the trails necessary to the successful establishment of such multidisciplinary treatment teams, as a model for managing this complex set of disorders.

References
Sex Assignment in Japan

Introduction
The first question that is usually posed by everyone who has been waiting for the birth of a baby is “is it a boy or a girl?” Because the appearance of the external genitalia is the major determinant of the social sex (gender), a newborn with ambiguous genitalia needs immediate and rational management. We should not delay clinical, hormonal, genetic, molecular and anatomical evaluation of patients with ambiguous genitalia. In the newborn with complex genital anomalies, the focus is now on accurate assignment of the sex of rearing. Culture plays an important role on sex assignment. Cultural difference in dealing with intersex individuals influences both the patient’s own psychosexual development and subsequent management. A multidisciplinary professional team approach is needed. Here, we outline our approach to the diagnosis and management of intersex children and consider the Japanese way of gender assignment.

Currently there are over 120,000,000 people in Japan. Compared to 50 years ago, the percentage ratio of young children is falling because of a decreased birth rate. However, the sex ratio of live births is almost stable. Although old people expect their first grandson as soon as possible, these findings showed there is no parents’ preference of sex of their children. An exception was seen in 1906 and 1966, which was the year called “Hinoe-uma.” It comes every 60 years in the oriental calendar. An old Japanese superstition said that women who were born in the year of Hinoe-uma eat men and they were hated as a symbol of bad luck. Therefore, the ratio of female babies born in Hinoe-uma year was extremely small.

It is estimated that the birth prevalence of complex genital anomalies where gender assignment may be difficult at birth is about 1 in 4500 births in Western countries. The existence of people who are neither ‘complete male’ nor ‘complete female’ has long been recognized in many societies. In Japan we also have an old word ‘Futanari’ which means ‘dual phenotype’ used for intersex conditions.

However in our society people are strictly categorized as male or female. Currently only two sexes are offered in Japan. Ahmed et al described that in some Western cultures, the distinction of gender is becoming less absolute and it may be better to consider these aspects as a continuum, with female characteristics at one extreme and male at the other. However, from birth to death the distinction is still absolute in our society. Unlike some countries, such as on the Indian subcontinent where gender diversity is associated with ritual powers, the acceptance of alternative gender may be difficult in Japan. At present a third gender is not a feasible option in our society.

Without an option of a third gender, early sex assignment is recommended. In Japan all babies have to get their family register within the first two weeks of age. Not only is their name required, but also sex and relationship to the parents, for example ‘first son’ or ‘second daughter’ must be entered in the register. Although registration of sex can be pending if there is medical reason, most parents are stressed both psychologically and financially. Many of them misunderstand that without family register no one can receive health insurance in Japan.

When the phenotypic appearance of the genitalia is ambiguous, a careful physical examination is required to reach a correct diagnosis. And appropriate biochemical, radiographic and chromosomal studies should be completed for early sex assignment based on a clear understanding of normal prenatal sexual development. However, measurement of some important hormones including Mullerian inhibiting substance, which are produced by the immature Sertoli cells, and molecular analyses are limited at most institutions, except for specialty centers.

We believe that one of the most important clinical factors in assessing the neonate with ambiguous genitalia is the evaluation of the gonads. First of all careful palpation is necessary. Even in the scrotum, if something is different from a normal testis, open biopsy should be done. Laparoscopy is useful to identify intraabdominal gonads as well as to evaluate the internal ductal structures such as uterus or genital duct. To make an accurate diagnosis, good understanding of typical gross appearance and histopathological findings of dysgenetic and/or streak gonads are necessary. For example in patients with mixed gonadal dysgenesis (MGD), you must investigate the opposite side of a streak gonad. Even if you can palpate normal testis in the scrotum, gross appearance is quite abnormal. In the histopathological examination of the streak gonad in MGD showed wavy ovarian like stroma. Primordial and primary follicles may be found, especially if examined in infancy. These findings are not indicative of true hermaphroditism. Dysgenetic testes are also typically found in patients with WT1 gene abnormalities, such as Denys-Drash syndrome and WAGR (Wilm’s tumor, aniridia, genital abnormalities and mental retardation) syndrome.

Let us show our basic way of decision making for sex assignment. First of all sex assignment should be done promptly but not haphazardly, sharing information on the diagnosis and management with the parents. Parents are advised that announcement of birth of the affected baby has to be postponed until a final decision is made. An experienced multidisciplinary professional team approach in the specialist centers is important. In our institute we established a ‘gender assignment committee’ for patients born with ambiguous genitalia. Main members of the committee are pediatric endocrinologists, pediatric urologists and medical social workers. Unfortunately Japanese pediatric psychiatrists are not as active as “Western countries.”

Our current management of intersex children is based on the following concept: sex assignment should be determined in the neonatal period. Genital surgery should be performed as early as possible. Re-evaluation of female genitalia is planned before puberty.

Our current management of intersex children is based on the following concept: sex assignment should be determined in the neonatal period. Genital surgery should be performed as early as possible. Re-evaluation of female genitalia is planned before puberty.

(continued on next page)
time of referral to us nearly half of them already had been assigned their gender. Five children who had an unsuitable gender assignment had to be re-assigned and their family register was corrected.

Conclusion

We take a conservative approach to the neonate with ambiguous genitalia according to the traditional paradigm.4,5

1. Urgency of diagnosis and sex assignment, so that early surgical reconstruction could obviate the fear of the parents with each diaper change.
2. Adequacy of the phallus as a male.
3. Fertility, especially in the 46,XX neonate with CAH.
4. Potential cosmetic appearance of the reconstructed genitalia.

With improvements in surgical techniques, cosmetic results are becoming less important. Now in Western countries, delayed sex assignment is recommended because they insist gender identity is the most important factor for gender assignment.6 Kipnis and Diamond have argued for a moratorium on nonconsensual genital surgery until more supporting evidence becomes available.7 However, the acceptance of intersexuality significantly differs between various countries. Japan is very conservative concerning gender and sexuality. For example, the first legally accepted genital surgery for the patient with gender identity disorder was performed in 1998 in Japan, only 7 years ago. Therefore, it is difficult and currently unrealistic to wait for children with disorders of sexual differentiation to establish their gender identity until 6 to 8 years of age. At present no one in Japan can raise a girl with a penis. However time goes by so slowly. Our future society may come to accept that all individuals with genital anomalies live as ‘intersex people’ and are treated as equals. Until that day comes, we think gender assignment soon after birth is recommended for children with ambiguous genitalia in our society.

References


Intersex: Sex Assignment in Singapore

Anette Jacobsen, M.D., Chief of Surgery
Kandang Kerbau Women and Children’s Hospital, Singapore

Singapore is a very small country, and our local experience is naturally not extensive. We have a multicultural and multiracial society, which is rapidly changing in virtually all aspects of life. This is reflected in our current management of intersex patients.

The birth of a child should be a very happy event for parents. “Congratulations, it’s a boy/girl!” is what they should hear. To hear anything different will be an absolute shock, and much of what we tell parents in the initial periods will not make much sense to them. We need to take this into consideration in the counseling of the parents. They can understand easily what they can see: what do the external genitalia look like. They can also understand in this situation what they know will be important: what are the chances of future fertility for the child. It is a lot more challenging to convey the concept of brain sex, enzyme deficiencies and genetics.

Who will influence the parent’s decision? In Asia the mother-in-law will have a lot of influence on decisions made. The child’s mother is commonly blamed for any imperfections, as she carried the child for nine months. We are reminded to dispel any such myths so as not to increase the pressure on mom especially and dad any further. Social pressures still exist to produce male, first born heirs. Legal and material processes favor males, and so do education and labor markets, although not to such a great extent.

Asian societies are still governed by Confucian values. The current generation has strictly traditional values, much in conflict with the next generation. It is still important to be a male in most Asian countries.

How then do we assist the parent in making an informed decision that we hope will stand the test of time, and is made in the best interest of the child and parents. We use a team approach, where the neonatologist, surgeon/urologist and endocrinologist make the initial evaluation.

The complete evaluation will include radiology, laparoscopy and biochemistry and genetics work up. We do not, to date in Singapore, have a dedicated psychiatric service to assist the parents and children (later), but we recognize an urgent and emergent need for interested and dedicated psychiatric support.

We need to assign a sex of rearing. Many schools are still segregated, toilets are segregated. A third sex will not be acceptable in our current society. This concept is a long way away from acceptance still.

The traditional decision of sex assignment will depend on the presence of a penis of adequate length. If not present, it is considered easier to create a vagina of adequate size for sexual function. Many papers have confirmed the malignant potential of dysgenetic gonads, which will need to be biopsied and removed. We would like to challenge the traditional concept, and realize we do not have all the answers. In rapidly changing times, we need to have a different approach, and perhaps be more broad minded in order that the decisions we make for the child with the parents today, will be relevant and appropriate in 20 years time too.

Our local experience with intersex patients at KK Hospital is limited, and a study of the series with outcome parameters is not meaningful. In the recent 8 years there have been a number of patients with severe proximal hypospadias. These will be all raised as boys after full evaluation. In cloacal extrophy we have raised one XY individual with concomitant spina bifida as a female. Our CAH patients are currently operated in the first year of life (N = 3) with a feminizing genitoplasty and clitoral recession. We have preferred to do the vaginoplasty in adolescence. Currently three new cases surfaced while preparing for the 7th APAPU meeting. They are not yet fully investigated, but one is

(continued on next page)
likely to be a mixed gonadal dysgenesis child with a male external appearance. The parents are very reluctant to accept any other outcome for this child echoing that their choice of rearing will more often than not depend on what they see as potentially functioning external genitalia.

The patients with CAH have all been raised female. In the clitoral recession the neurovascular bundle is preserved, and the corpora amputated allowing for recession. The skin is refashioned in a standard manner. Our decision will have to be based on the best evidence available at this time, and we can only hope that this will be the correct decision that will stand the test of time.

If fertility can be achieved via artificial means if not naturally, we then have to consider future sexuality and sexual function in a different light. Even Singapore which is a very conservative country with rigid rules governing pornography and “alternatives” to mainstream culture and publications, have recently held an “Adults only” exhibition called Sexpo. This exhibition features erotic toys and furniture to enhance love making. I think the accepted norms are being challenged worldwide, and we have to follow.

We have to go back to Hippocrates in order to choose correctly for the next generation. “First, do no harm.” To me this implies limiting mutilating surgery, and anything irreversible if the choice later has proved to be incorrect. Sex of rearing will have to be assigned in consultation with parents and all specialists involved in a consultative manner. Our decision will have to be based on the best evidence available to us at this time, and we can only hope that this will be the correct choice in the future for the child. Asia cannot consider itself in isolation – we are all connected in so many ways, and our decisions should be no different from elsewhere. Our data and outcomes should be measured systematically using simple classifications and outcomes measures, which will give us evidence based data for future use.

**References**

Sex Assignment in Taiwan

A hidden disease in the past

In order to gain a better understanding of the status of sex assignment in present day Taiwan, we organized an interdisciplinary team of physicians consisted of pediatricians, pediatric surgeons, psychiatrists and endocrinologists from major medical centers in northern Taiwan. We studied patients who received our treatment in the past to devise a strategy for managing intersexual patients in the future. A simple survey of endocrinologists and gynecologists for adults was done as a preliminary study to understand the current condition of adult intersexual patients. Surprisingly, among those surveyed only 5 patients or less were followed up inconsistently in each of the largest five medical centers in northern Taiwan. We then contacted the phone consoling station, which is very popular in Taipei for the anonymous call-for-help service it has provided for the past 30 years. The counselors there have extensive experiences discussing homosexual or transsexual issues with people who need help. They denied of any call from intersex clients in the last 20 to 30 years.

However, a recent nationwide screening of newborns in Taiwan revealed that the incidence of congenital adrenal hyperplasia (CAH) was about 1 in 20,000. The simultaneous CAH genetic study showed that the incidence of heterozygous carriers was about 12 in 1,000, and in the Chinese population the incidence was 1 in 28,000. Because three quarters of CAH patients suffered from salt-losing which might cause mortality in their infancy, excluding those patients, we estimated that there should be more than 300 intersexual patients evenly distributed in each age group with a population of 23,000,000 in Taiwan. The genetic diagnosis of intersexuality other than CAH was not as straightforward. Before the biochemical markers were developed, the diagnosis of intersexuality relied solely on chromosomal analysis. Only 9% of the patients were explicit diagnosed before the year 2000. The number has risen to 64% since the biochemical analysis for androstenedione (ASD), dihydrotestosterone (DHT) and the molecular diagnosis for androgen receptor (AR), SRD5A2, WT1, and SOX9 became available (Fig. 1). The rarity of intersexual patients encountered in hospitals and public psychosocial consultation services might be due to the insufficient data to support the genetic diagnosis of intersexuality in the past 20 years. Another major factor might be cultural or behavioral. Chinese patients might feel uncomfortable and insecure discussing sexual matters with their doctors. People do not like to talk about their subconscious problems when they are not convinced that the doctors have any way to help. The absence of complaints in consultations did not mean that patients do not have any sexual problems, however.

Present practice in sex assignment

Gender assignment is made in early infancy. Pediatric endocrinologists, pediatric surgeons, neonatologists and genetic specialists are all involved, but not psychiatrists, nor social workers. Parents are also involved in the evaluation and the decision on sex assignment. In our practice all CAH patients are assigned as female (regardless of the degree of virilization), while all hypospadias and micropenis patients are determined to be male. The assignment of other intersex infants relied mainly on the appearance of the genitalia in the past, but today the actual genetic diagnosis is the deciding factor (Table 1). Some of the parents withhold diagnostic details from the children. Feminizing genitoplasty surgery with one stage vaginoplasty is done between 3

Figure 1 - Major Event Related to Intersex in Taiwan

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Karyotyping</td>
<td>1977</td>
</tr>
<tr>
<td>High Resolution Banding</td>
<td>1992</td>
</tr>
<tr>
<td>SRY Gene Detection</td>
<td></td>
</tr>
<tr>
<td>Biochemical Analysis for Androstenedione (ASD)</td>
<td></td>
</tr>
<tr>
<td>Biochemical Analysis for Dihydrotestosterone (DHT)</td>
<td></td>
</tr>
<tr>
<td>Molecular Diagnosis for Androgen Receptor (AR)</td>
<td></td>
</tr>
<tr>
<td>Molecular Diagnosis for SRD5A2, WT1, SOX9</td>
<td></td>
</tr>
<tr>
<td>Psychological Assessment for Long Term Prognosis</td>
<td></td>
</tr>
</tbody>
</table>

(year)
months and one year of age. Most pediatric surgeons continue to recommend sex assignment at early infancy according to our recent questionnaire.

**Psychiatric evaluation of teenager and adult CAH patients**

All patients who visited pediatric clinics with a diagnosis of CAH were contacted by phone from July 1 to September 30, 2005. Ten patients who were older than 12 years consented to participate in our psychiatric evaluation. The age of diagnosis and operation, the degree of virilization, and the gender preference of the families were obtained from medical records. Although the patients recalled that they recognized more masculine gender activities during childhood, all of them felt that they made the right decision to date. Patients and parents were assessed for the subjects’ psychosexual development. Patients’ behavioral and emotional problems were evaluated with Child Behavior Checklists (CBCL). Patients completed self-report questionnaires that included Body Image Questionnaire, Quality of Life (PedQoL or SF-36 health questionnaire), CHQ (Chinese Health Questioner). The patients’ psychopathology, gender identity and sexual orientation were assessed by a semi-structured interview, conducted by child psychiatrists.

The scores in PedQoL of all patients were within the normal range. However, there was a difference in the quality of body image in comparison with the norm. One patient suffered from gender dysphoric disorder and was bisexually oriented; another patient suffered from gender identity disorder and was homosexually oriented. Six patients had lower scores in the appearance evaluation and appearance orientation of their body image. The body image problems occurred in the adolescent period when their appearances became more masculine as a result of hormonal abnormalities. Intimate relationships were deeply impacted as a result of the masculine appearances. Our patients were also more dissatisfied with their body image and paid less attention to their appearances. Four patients were dissatisfied with their lower torso and body weight; three of them were also dissatisfied with their upper torso and height.

The parents also showed high CHQ scores (5 out of 9 parents scored higher than the cutting point), suggesting their higher susceptibility for minor psychiatric diseases. These parents never sought psychiatric intervention, but they had intense worries about the patients’ illness and their future. When the parents were more informed about this illness, their rearing skill became more gender oriented, and their children tended to show more gender appropriate role play as a result. In the two patients with delayed diagnosis, one parent ignored the illness and avoided any intervention. That patient showed gender confusion in adolescence.

This is a pilot study for understanding the adjustment, gender identity and body image of patients with CAH in Taiwan. During the interview with these ten patients, we noticed that early diagnosis followed by adequate intervention and illness education for parents and patients resulted in better adjustment mental health later in life. Our patients with delayed (adolescent) diagnosis had more obvious negative body image and poorer mental health when compared to the CAH patients with early diagnosis and continuous intervention.

(continued on next page)

| Table 1: Gender assignment in intersex other than CAH |
|---------------------------------|---|---------------------------------|
| **Undervirilized male (XY)**    | 30 | Gender Assignment |
| True hermaphroditism            | 3 | 1 male, 2 females |
| Gonadal dysgenesis              | 7 | |
| Pure (XY)                       | 5 | All female |
| Mixed (XX/XY)                   | 2 | 1 male, 1 female |
| Camptomelic dysplasia           | 2 | females |
| Denys-Drash syndrome            | 1 | females |
| Leydig cell hypoplasia          | 4 | All females |
| Testosterone biosynthesis defect| 0 | |
| Androgen insensitivity syndrome  | 9 | |
| Complete form                   | 4 | All females |
| Partial form                    | 5 | 2 males, 3 females |
| 5-alpha-reductase type 2 deficiency| 2 | All males |
| Persistent mullerian duct syndrome| 1 | male |

| **Virilized female (XX)(exclusive of CAH)** | 4 |
| SRY (-)                                     | 3 | 2 males, 1 female |
| SRY (+)                                     | 1 | males |
Evaluation of one stage vaginoplasty

The most commonly identified anatomical problem after surgery is a posteriorly located and small opening of the vagina. Nine out of twelve teenagers were examined. The vaginal introitus was stenotic and the clitoris was either small or absent. A repeat vaginoplasty was recommended.

Conclusions

We recommend providing the following services to improve patient outcome in the future:

1. Offer psychiatric and psychological consultation for the parents and patients. The team work in sex assignment should include psychiatrists and social workers. The dominant role of the surgeons may have to be changed in the future.

2. Organize a parents and patients forum to discuss and exchange information freely.

Gender Assignment in Intersex – The Korean Experience

Sang Won Han, M.D., Professor of Pediatric Urology
Yonsei University Medical School, Seoul, Korea

The words “gender” and “sex” used to be interchangeable but these days the difference between the two words are becoming more and more apparent since the word “sex” refers to the biological aspect such as having female genital organs or 46XX, whereas “gender” implies the social aspect including gender assignment, gender role, gender identity, gender attribution and sexuality. Gender socialization starts from gender assignment which occurs at birth, followed by gender role where he or she express their individual gender role behavior according to the society’s expectation.

Gender identity refers to the individual perception of one’s own gender and how it fits into the gender role in society. Gender attribution is what we do to decide whether a person we have just met is a man or a woman. Gender identity is the most important element in this process. If he or she is raised with the wrong gender assignment, one will fail to form an appropriate gender identity and will not able to adapt to one’s society, and ultimately their gender might have to be reassigned.

What affects the gender identity?

There are a lot of genes which decide or act on sexual differentiation, however, these merely result in the production of sex hormones and phenotype at birth. Genes are responsible for hormone production and their metabolism, eventually influencing the phenotype and brain sex. We assign gender for patients, rear them according to sex, perform hormonal manipulation and genitoplasties all in the expectation of the patient to perceive their appropriate gender identity. In other words, phenotype, brain sex and our efforts altogether affect the attainment of gender identity.

In 1999, Dr. Zucker reported that gender identity does develop in the absence of gender specific genitalia in his long-term follow-up study of intersex. In addition, Dr. Berenbaum suggested that gender identity in CAH is not related to the degree of genital virilization. Today, the actual genital appearance may not be as crucial in developing gender identity as it once was thought to have been. Although not subjected to intersex patients, a group at Johns Hopkins reported that cloacal extrophy children born genetically and hormonally male, identified themselves as males despite being raised as females and undergoing feminizing genitoplasty and orchiectomy at birth. Therefore hormonal manipulation with genitoplasties and sex rearing may not change the sex which has been decided during the fetal period.

There have been studies reporting that prenatal and neonatal (sex) hormonal manipulation changes the reproductive behavior and sexual differentiation in rodents. Similarly, female birds which have been neonatally masculinized sing like male birds in adulthood. One can say that brain sex is determined by fetal and neonatal sex hormones in rodents and birds. The neonatal period in these animals corresponds to the third trimester of human pregnancy.

In 1993, we determined that neonatal androgen replacement after castration can prevent cell death of sexually dimorphic nucleus in rats. Although there is no experimental data in humans, there are many clinical scenarios supporting the importance of brain sex. Females with CAH are exposed to androgen during gestation and although a majority of them have female gender identity and even if the adrenal androgen is successfully suppressed, they generally have tomboyish personality. This is supported by a systematic examination of the relationship between genital appearance and gender identity in a group of girls with CAH where a link between atypical gender identity and prenatal androgen exposure has been shown, but not with the degree of virilization.
Similarly, patients with 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency assigned with female gender often want to become male at puberty and patients with complete androgen insensitivity (XY female) do not show male characteristics. Therefore, brain sex would be the most important factor influencing the gender identity in humans.

In humans, testosterone surge occurs 3 times from the time of conception to death. The first one is from 8 weeks to 24 weeks of gestational age, the second is during infancy and the third is during puberty. The differentiation of genitalia conforms to the first testosterone surge. Unfortunately brain sex does not correlate with the phenotypic sex and the possible explanation for this has been suggested that the critical period of the androgen receptor activation in the CNS may differ from the testosterone surge. Another possibility is Hutson’s thesis that infantile surge of testosterone is responsible for the second androgen imprinting in the CNS. According to his thesis, infants who are diagnosed late or treated beyond ages of 4-6 months should not undergo sex reversal operations. However, the Johns Hopkins group performed orchietomy at birth and showed that once a male is always a male in spite of neonatal orchietomy. Brain sex is obviously the most important factor affecting gender identity.

Gender assignment in intersex in Korea

A survey was performed of 17 Korean pediatric urologists, all having significant experience in managing intersex. We classified into 4 categories; virilized XX, undervirilized XY, true hermaphroditism and mixed gonadal dysgenesis. We then asked a series of questions on management.

Virilized XX

A virilized XX baby results from exposure to fetal and maternal androgen and CAH is the most common cause. They should be assigned as females since they may have a potential for normal sexual function and fertility although their brain sex may not be completely female. Most of these patients ultimately attain female gender identity although there is a high incidence of bisexuality and homosexuality.

1) Have you ever assigned a 46XX CAH patient as male?
All except 2 Korean pediatric urologists who participated in the survey answered that they have and would assign CAH patients female. The two exceptions were due to late diagnosis and the fact that they have already been raised as males.

2) When do you perform clitoroplasty in CAH?
Ten pediatric urologists answered 6 months to 1 year old, 4 said after 1 year but before school age, and 2 answered during school age and puberty.

3) When do you perform vaginoplasty in CAH?
One third answered that they performed vaginoplasty simultaneously with clitoroplasty before the age of 1 yr, another third performed it before puberty and 5 urologist answered after puberty.

Three doctors said that they perform initial surgery during infancy and perform a redo-vaginoplasty after puberty.

Undervirilized XY

An undervirilized XY baby is the most difficult part of gender assignment. There are two typical groups; the androgen insensitivity syndrome group (AIS) and the enzymatic deficiency group.

Androgen insensitivity syndrome is caused by a x-linked mutation in the androgen receptor (AR) gene and can be either presented as complete insensitivity (testicular feminization) or partial insensitivity, also known as Reifenstein syndrome.

Patients with complete AIS should be assigned female.
Their external genitalia are undoubtedly female and brain sex must be female because the androgen receptor in the brain is also deficient. Testes can be removed at diagnosis or preserved until puberty but must be removed after puberty.

1) When do you perform orchietomy in complete AIS?
Nine answered at diagnosis, 6 said they wait until after puberty to avoid estrogen replacement and one doctor answered that he follows his patients without orchietomy.

Patients with partial AIS are more often assigned as female than male.
However, their brain sex and response to testosterone may be diverse, therefore, the response to testosterone must precede assignment. In addition, there have been reports of fertile male in milder forms of partial AIS.

2) Which factors do you consider important in assigning gender in partial androgen insensitivity SD?
Korean pediatric urologists pointed out phenotype as the most and response to androgen as the second important factor and regarded brain sex as the third important factor.

Gender assignment in patients with enzymatic deficiency involving the production and metabolism of testosterone (i.e., 5 alpha-reductase, 17b-hydroxysteroid dehydrogenase) can be controversial. However, they should rather be assigned as males due to the following reasons.
The brain sex is determined not by dihydrotestosterone (DHT) but by testosterone, so the brain sex could theoretically be male and even if they are raised as females, some of them eventually change their gender role from female to male. In addition there is considerable virilization with good erections at puberty in males with the help of the third testosterone surge and occasional fertility in males have been reported.

On the other hand, the rationale for female gender assignment in enzyme deficiencies is that they sometimes need mastectomy after puberty and following Hutson’s thesis, early orchietomy might prevent second androgen imprinting in infants.

1) Do you measure DHT level for gender assignment in enzymatic deficiencies?
More than half of the Korean pediatric urologists said they did.

True hermaphroditism

True hermaphrodites can be found with both testicular and ovarian tissue with germ cells. The most common form is having two ovotestes, but the combination of either an ovotestis and an ovary or a testis and an ovary can also be found. Patients with true hermaphroditism can be assigned to either sex. There is lack of report regarding the long-term follow up results of true hermaphroditism. Brain sex may vary in each case. If

(continued on next page)
From the results of this survey, it could be concluded that Korean pediatric urologists were more concerned about the phenotype and growth of external genitalia rather than brain sex or socialization affecting gender identity. From the results of this survey, it could be concluded that Korean pediatric urologists were more concerned about the phenotype and growth of external genitalia rather than brain sex or socialization affecting gender identity. The reason for these results might be because they regarded these issues with a surgeon’s point of view. Most pediatric urologists said that neonatologists and pediatric endocrinologists participate in gender assignment in neonates as well as pediatric urologists. However, they would like the opinion of a psychiatrist when they have to reassign gender.

Korean pediatric urologists seemed to understand the biological behavior of intersex and they seem to bend their efforts to get the opinion of psychiatrists. The importance of early gender assignment and early recognition of brain sex which has been gradually increasing, can be found in the recently published papers. However, we can only theoretically suggest the significance of brain sex. Further studies and investigation of methods to recognize brain sex (androgen imprinting) in neonates are warranted.

References

raised these patients are raised as males, spermatogenesis / androgen production will be deficient and would require regular evaluation for testicular tumor. On the other hand, if raised as females, ovaries may ovulate and there is a chance that the patient might become pregnant.

1) What are the factors they considered important in gender assignment of true hermaphroditism?
   Phenotype, chromosome and presence of a gonad were the top 3 important factors and regarded brain sex and fertility less significant.

Mixed gonadal dysgenesis
Patients with mixed gonadal dysgenesis(MGD) can be assigned as either male or female.

Dysplastic testes, streak gonad, gonadal asymmetry with mostly right side male and 45X/46XY are characteristic of MGD. The brain sex would be male, but the ultimate size of the penis is usually small and height of a full-grown adult is short due to a Turner phenotype. Fertility cannot be expected.

1) What factors do you consider important in gender assignment of MGD?
Korean pediatric urologists pointed out phenotype as the most important factor in gender assignment and they have less concern regarding brain sex, socialization and height or sexual function.
ORDER YOUR SUBSCRIPTION TODAY!

The SPU is pleased to offer subscriptions to Dialogues in Pediatric Urology. Members of the SPU receive a complimentary subscription to Dialogues.

Non-Members can subscribe at the following rates:

- Domestic subscriptions (within the United States): $75.00 per year.
- International subscriptions (including Canada and Mexico): $100.00 per year.

Dialogues is published on a bi-monthly basis and distributed to all subscribers in both print and electronic format. Subscribers will also have access to past issues of Dialogues via our online archive system.

Name: ____________________________________________________________

Address: ____________________________________________________________________________________________

Address: ____________________________________________________________________________________________

City/State/Zip: ________________________________________________________________

Telephone: ___________________________________________________________________ Fax: ___________________ 

E-Mail: __________________________________ Date of Birth: ________________________

(Necessary for secured access online.)

Payment Method:

- [ ] Amex  - [ ] Mastercard  
- [ ] Visa  - [ ] Check amount enclosed: $__________

Amount to be charged: ________________________________________________________________________________

Credit Card Number: ____________________________________________ Exp Date: ________________ 

Authorized Signature: ___________________________________________ Security Code__________

3 or 4 digit number on the front or back of your card

Complete and return with payment to:

Society for Pediatric Urology, 900 Cummings Center, Suite 221-U, Beverly, MA 01915
Tel: (978) 927-8330 / Fax: (978) 524-8890 / E-Mail: spu@prri.com
INSIDE THIS ISSUE......

Intersex: Sex Assignment in Asia

Guest Editor: Saburou Tanikaze, M.D.

The challenges of gender assignment in several different Asian cultures including:

♦ Japan
♦ Singapore
♦ Taiwan
♦ Korea

Special commentary by William Reiner, M.D.