

Virtual Mentor

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Clinical Case

Partial Androgen Insensitivity Syndrome

Commentaries by William G. Reiner, MD, David A. Diamond, MD, and by Tammy Camp, MD, and Surendra K. Varma, MD

While delivering Mrs Burdett's third child, her obstetrician observed that the baby had ambiguous external genitalia; on the evidence of the labioscrotal folds and incompletely formed penis or clitoris, the baby's sex could not be determined on sight. The obstetrician calmly answered the Burdetts' question about whether their new baby was a boy or a girl by saying that some further examination would be needed. Then he called in Dr Leclerc, a pediatric endocrinologist, to explain the situation to the Burdetts and help them decide on their next steps.

Genetic tests performed the next day revealed that the baby had a 46,XY karyotype. Based on this and on the ratios of testosterone to luteinizing hormone and to dihydrotestosterone, the Burdett newborn was diagnosed with partial androgen insensitivity syndrome (PAIS). When the Burdetts learned of the diagnosis, they were sad and nearly speechless. Neither had ever heard of such an occurrence before. Dr Leclerc told them that the condition was not extremely rare and that parents of babies born with PAIS had taken a variety of approaches; some parents designated a sex for the newborn immediately and had surgery performed on the external genitalia if necessary. Other parents chose to wait until the child grew some and developed characteristics that appeared to favor one gender identity over another. But Mr Burdett protested, "I don't understand. If our child has XY genes why doesn't that make him a boy?" Dr Leclerc had been asked these questions before and knew that an overly medicalized answer would not be satisfying. He told the Burdetts that the decision about how to treat a child with PAIS was complicated by many factors beyond DNA and hormones. Understanding that Mr and Mrs Burdett were devastated by the confusion over their newborn's sex, Dr Leclerc wanted to give them all the information and options he could without making the process even more difficult. He knew, though, that most parents in the Burdetts' position ended up asking him what he would do if the child were his.

Commentary 1

by William G. Reiner, MD

Dr Leclerc is in a unique position. He has the potential to mitigate the Burdetts' anxieties about their child's present and future growth and development while designing both a short-term and a long-range outline that can initially guide the parents and later the child. Within this framework he can begin to establish a trusting, open, and, presumably, mutually satisfying relationship. The care plan should be organized and written in a schematic format with new information and details added

as they become available—the child's case is too complex to rely solely on parental memory. This written outline will then become a readily accessible reference for the Burdetts and everyone involved in Baby Burdett's care. Schematics, such as charts, maintain a visual focus for clinical discussions over time. The framework should establish:

1. The overall clinical picture.
2. The clinical approach.
3. A plan for following the baby and the parents over time.

Using these techniques Dr Leclerc can gradually incorporate all clinical data, pertinent information, and answers to the Burdetts' questions into the clinical record as they arise, while the corresponding schematic will allow the parents to have ongoing access to their child's assessment and test results. This reference will also be helpful for all other physicians who see the baby. Dr Leclerc can immediately explain their baby's clinical picture to the Burdetts and can share information on the baby's overall growth and development as it occurs. But he must stress that he cannot predict their child's gender identity with accuracy.

Establishing the Overall Clinical Picture

The clinical picture of any given child begins with conception. Most of the genome is active in embryonic and fetal neuronal development. Precise gene functions or actions in brain development are mostly unknown, and it is important to emphasize to the parents that none of us ever really knows quite who or what our child is or will be at the time of its birth or how he or she will develop after birth, much less during gestation. Part of the joy and excitement, as well as the anxiety, about child rearing is this unpredictability, and any added unpredictability in a child with an intersex condition does not diminish the child. On the contrary, such a human variation may enrich the child's life experience (although discussions of such a plausible development may not readily relieve typical parental anxieties at this time).

Physiologically speaking, the karyotype of the child is important, but causality of gender identity is separate from karyotype and has not been delineated. The Burdetts should be informed that the exact function of the genes on the Y chromosome and their actions in mediating the sexual differentiation of the brain are unknown. What is known and what the parents must know is that the presence of the Y chromosome by itself does *not* lead to a male gender identity.

In fact, few general relationships between sex-specific phenomena and their influences on gender identity have been discerned for typical children, let alone for children with intersex conditions. For example, the importance of the timing of prenatal hormonal effects on human brain development, or even dose-response relationships, is only poorly understood. Gender identity is a reductionistic construct that presupposes some knowledge of what identity, itself, means beyond the purely subjective and intuitive. Any concept of gender causality must preserve, explicate, and satisfy our human intuitions about what gender is.

During post-gonadal fetal development, this baby was exposed to substantial levels of androgen, but, because of the baby's partial androgen receptor defect, much of this androgen exposure was ineffective for establishing definitive male sexual differentiation. Some active androgen exposure was experienced and achieved real, but presently unknown, interactions with (other) direct or indirect Y-chromosome-induced functions.

After noting the clinical data presently available in the written outline, Dr Leclerc should convey what further data might be helpful and explain that the quantity, quality, and the timing of prenatal androgen exposure probably has a different relationship to brain development than it does to genital development—that is, the brain and genitalia do not necessarily have either synchronous or corresponding development. Then Dr Leclerc should interpret the clinical situation for the parents in lay terms: sex-assignment is important for this child, but the assigned sex may be discordant from the child's ultimate recognition of its gender.

Dr Leclerc can discuss their baby's diagnosis and the lack of urgency in this case (because of the absence of metabolic abnormalities). He can explore the parents' support systems including extended family, friends, and social contacts. He should also provide outside resources for the family. This can include a child psychiatrist, a pediatric urologist, and a nurse with specialized interests in developmental genital anomalies. Dr Leclerc can provide the names of willing individuals with similar conditions or parents in similar situations; he can direct them to web-based information for androgen insensitivity-specific or more generalized intersex support groups. Finally, Dr Leclerc can reaffirm that, despite the apparent ambiguity, their baby will know who he or she is.

Establishing the Clinical Approach

A team approach to managing Baby Burdett is indicated because of the complexity and multispecialty needs of this child. The Burdetts should be encouraged to interview each of the assigned specialists. Dr Leclerc or one of the other specialists should be designated the chief spokesperson for the team. The specialized nurse would be an ideal contact and coordinating person for the parents. Other specialized personnel may not be based in the hospital, so communication or consultation with them would frequently be by telephone or e-mail. The nurse-specialist is in a good position to coordinate rapid communication among these consultants and the Burdetts.

Establishing the Plan for Following the Baby Over Time

Short- and long-term plans should be established for following the baby and the parents. The outline and schematic chart will be updated whenever new information is available or decisions are made. The parents can record their own observations during their baby's growth and development in this chart. This follow-up plan provides a flexible approach for coordinated reassessments of the child at specific intervals. By providing routine input from the parents, the child, and from each of the subspecialists, the plan also encourages flexible clinical and parental strategizing as the baby's overall identity unfolds.

Unforgiving interventions should be discouraged until longer-range clinical goals are clear. One must be prudent in recommending surgical reconstructions—for that which is removed cannot be replaced. Dr Leclerc should emphasize that non-excisional reconstructions can always be undone at a later date if the child so desires, but tissues that are excised are lost. Vaginal or phallic reconstructions, for example, generally remove nothing, while genital or gonadal excision is permanent. The timing of surgery is less important than whether the surgery chosen is in the child's future best interest. Reproductive potential is a risky parameter for assigning sex. Virtually all people are sexual, but not all are reproductive. Some cannot reproduce, some choose not to, and some prefer that their mates carry out reproductive chores without their participation. A child's future (adult) desire for or rejection of reproduction is unpredictable and, hence, a poor guide for early sex-assignment decision making.

Conclusion

The central theme of this approach to a baby with an intersex condition, then, is that only a given person can know who he or she is. As with each of our children, we parents must learn to adapt to our children as we (and they) begin to recognize who they are, and we must assist them in those developmental tasks and needs peculiar to each of them. Flexibility in our approach is critical because the ambiguity of the situation is ours, not the child's. The anxiety about the ambiguity is also ours. The child's privacy is important, but secrecy may be counterproductive. Indeed, as in many vital situations, openness with the child can aid in developing important bonds of mutual trust and communication between parents and child, parents and physician, and physician and child. Clinical data are unlikely to remain a secret forever. Ultimately, the parents must make the decision about initial assignment of sex, for social and legal reasons, generally within a few days of birth of the baby to about 1 to 2 weeks of age. It is important that the child's physicians aid in this decision-making process. It is also important that the child's physicians respond sensitively and remain available to the parents and to the child, over the time of the child's growth and development.

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Commentary 2

by David A. Diamond, MD

The obstetrician and Dr Leclerc have handled this difficult situation well by maintaining a calm and honest approach with the parents over the newborn child's ambiguous sex. The first order of business in the management of this child's care should be to make a definitive diagnosis of the specific intersex disorder. Based on karyotype and endocrine studies, the child appears to have a partial androgen insensitivity syndrome. This diagnosis can be further confirmed by PCR analysis of venous blood for chromosomal abnormalities of the androgen receptor. One means of explaining the abnormality to parents is to tell them that, despite an 46,XY

karyotype and the presence of a male hormone, the tissue is unable to "recognize" the hormone as it would under normal circumstances.

Findings from the physical examination and work-up need further clarification. The presence and position of gonads should be defined. The size and anatomy of the penis/clitoris and labioscrotal folds should also be determined to confirm the degree of virilization, and an abdominal ultrasound should be done to confirm absence of mullerian tissue.

The management issues for this newborn include sex assignment and appropriate treatment of the gonads and external genitalia. Partial androgen insensitivity, unlike complete androgen insensitivity, is an intersex condition for which no general consensus exists as to the better sex assignment. In other words, either sex may be assigned based on the anatomic findings. Indeed, a recent study of a modest number of partial androgen insensitivity patients raised as male or female demonstrated long-term satisfaction with either sex assignment [1]. Thus, more than 1 scenario is possible with this patient. One option may be to assign sex in the newborn period and carry out sex-appropriate surgical reconstruction.

If the decision were made to assign male sex to the child, hypospadias repair and scrotoplasty could be performed at 10 to 12 months of age. Undescended testes would require orchidopexy at this time. Although infertility is anticipated with partial androgen insensitivity, the potential for assisted reproductive techniques would be preserved.

If female sex were assigned, female genital reconstruction and gonadectomy could be performed after 6 months of age. The child would be infertile, and estrogen replacement would need to be started at the appropriate time to initiate puberty.

An alternative approach is to delay surgery for as long as possible with the hope that the child may develop a gender identity. In cases such as this, one could remain neutral until the time of anticipated puberty. Once pubertal stimulation occurs, however, the child would be virilized by the existing testes and a female sex assignment would be forever compromised. So, realistically, a relatively early decision must be made.

There are, however, risks to surgical reconstruction, the major one being an irreversible alteration in anatomy that may prove to be inconsistent with the child's developing gender identity. The technical outcomes of early reconstructive surgery have been criticized in some studies, but techniques have steadily improved, and an operation performed 30 to 40 years ago bears little resemblance to the surgery being performed today. Thus, surgical outcomes research based on the current adult population is imperfect, at best. There are also risks to deferring surgery, independent of pubertal virilization. The psychological consequences of being genetically ambiguous until age 10 or 11 is unstudied, but there has been wide speculation of distress associated with lengthy delays. Whichever course is taken, a team approach to managing Baby Burdett—including endocrinologists, urologists, and psychiatrists—is highly recommended.

Ethical Concerns

The ethical issues raised by a case of partial androgen insensitivity include respect for autonomy and surrogate decision making, the meaning of informed consent, conflict between autonomy and beneficence, and veracity on the part of the treating physicians. The newborn with ambiguous genitalia must be regarded as a nonautonomous patient with the *potential* for autonomous decision making. Thus, appointment of a surrogate decision maker—most likely the parents—is necessary for decisions related to the infant's care with the understanding that, upon sexual maturity, the child will have developed a gender identity and gender orientation (choice of sexual partner). These gender decisions are unpredictable and may differ from the sex assigned by the parents and medical team years before. The standard most commonly applied by a surrogate for the pediatric patient is the "best interests standard," but in cases as complex as these, predicting what will be in the best interest of the future child is challenging for parents. This places a burden on the treating physicians to educate the parents sufficiently so they can act as responsible surrogates, capable of providing informed consent.

In a previous era, under the paternalistic model of a physician-patient relationship, physicians assumed a large—perhaps too large—a role in decision making for the infant. This attempt at beneficence usurped autonomy from the parents and has been a source of anger and frustration to some families many years after the treatment decisions were made. Honesty and good clinical judgment on the part of the treating physicians are essential for a trust-based relationship with the parents and, ultimately, the child. With these children, for whom medical science may be incapable of assuring a "right approach," physician transparency and humility seem especially appropriate. In addition, ongoing mutually trust-based relationships between the treating physicians and the maturing patient are critical in respecting the autonomy of the patient and avoiding the anger and shame experienced by some intersex patients whose diagnoses have been forced to remain secretive.

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Commentary 3

by Tammy Camp, MD, and Surendra K. Varma, MD

Cases of ambiguous genitalia are encountered by obstetricians and pediatricians with some frequency, and these health care professionals are often at a loss as to what to

tell the parents. Although pediatric endocrinologists are familiar with this dilemma, no guidelines apply to all cases; each must be considered unique.

When a baby is born with ambiguous genitalia, the parents immediately face a social dilemma. Extended family members waiting outside the delivery room and at home are anxious to know whether the baby is a “boy or a girl.” In cases of ambiguity, what should be the answer? During this time of confusion, the medical team should be cautious, using phrases such as “your baby” or “your child” rather than “he” or “she.” The infant’s genitalia should be shown to the parents, and the findings should be explained to them by the pediatrician and the pediatric endocrinologist. While the medical team may easily accept that the sex cannot be determined at this time, the sensitivity of the situation and the parents’ dilemma about what to tell the family should be considered and discussed.

Parents generally feel relief when they share the burden of a child’s physical anomalies, such as cardiac abnormalities or even facial clefts, with extended family. Unfortunately, because of its delicate and sensitive nature, parents often feel embarrassed to say that the sex of their new child is undetermined. Although there is no single “right” answer as to what parents should tell the extended family, it is our experience that parents are at greater ease if they share with their loved ones the fact that physicians are still determining the sex of the baby and that it may take a couple of days to do so because the external genitalia of the infant are not well defined.

Society’s concern about sex assignment is not a new phenomenon. Universally, one of the first questions asked after the birth of a baby is, “Is it a girl or a boy?” Throughout history, societies have been intrigued by the physical and psychosocial intricacies of reproduction and the roles of the sexes. Hence, the appearance of ambiguous anatomy is confusing and troubling.

Despite our current knowledge of the genetic and biochemical factors involved in the regulation of sexual differentiation and our ability to determine the physical adequacy (or inadequacy) of the genitalia, our approach to management of this abnormality remains problematic.

The inability of some genetic fetal males to masculinize sex duct development in external genitalia, as has happened in this case, can be divided into 2 groups: (1) a fetus that is unable to produce sufficient amounts of testosterone and dihydrotestosterone, or (2) fetal tissue that is unable to respond to and absorb androgens that are present in normal amounts [1].

Normal sexual differentiation requires the coordinated interaction between chromosomes, gonads, hormones, anatomical structure, and psychobehavioral factors. All of these factors combine to develop male or female characteristics. Infants with ambiguous genitalia are generally evaluated by a multidisciplinary health care team that includes a pediatric endocrinologist, geneticist, pediatric surgeon, urologist, ethicist, social worker, psychologist, psychiatrist, and nurses. After a comprehensive evaluation of the infant, this team assumes, along with the parents, the responsibility of assigning

the child a male or female sex and initiates a short- and long-term management plan, including medical and surgical treatment. In the past, the health care team's approach was more paternalistic and usually provided the parents with only basic information about the pathophysiology and possible cause of their baby's ambiguous genitalia. In our experience, it has been critical to involve the parents in the decision-making process.

The factors considered for proposing sex assignment include the size of the phallus and, most importantly, how this infant will be able to function as an adult. The judgment as to whether the baby would be better off as a nonreproducing, sexually functioning woman or a sexually impotent man possibly *with* reproductive capabilities must be made with careful evaluation, sometimes necessitating a second opinion [2]. It is desirable that the individual be able to function sexually with or without intercourse and that the individual be able to realize satisfaction and pleasure from sexual relations and activities. If necessary, psychiatrists or psychologists can help stem, avert, or manage dysphoria or psychiatric disturbance resulting from the condition.

Surgical correction should be carefully planned. It should be done by the time the infant is 6-12 months old so that as a toddler, the child does not consider himself or herself different from other children of the same age. We have learned that the goal of treatment should be to promote existence of an individual who is satisfied with his or her physical appearance and has a good quality of life.

It should be emphasized again that, even among infants with the diagnosis of partial androgen insensitivity, every child and family need to be evaluated individually. A child's sense of maleness or femaleness is not fixed at birth. Parents should be given accurate, easy-to-understand information, and ample time to help decide the sex of their newborn without feeling pressured to make a hasty choice. It should be explained that ongoing care and treatment will be required throughout the baby's childhood and perhaps on into adulthood. Medicine has not been able to provide all the answers or solve all of the problems associated with PAIS. There is some debate about whether it would be better for these individuals to make their own sex assignment decisions and, if so, when that decision would best be made. It is also debatable whether parents should bear the ultimate responsibility for making treatment and sex assignment decisions for their infant child [3].

It is hoped that, with advances in surgical techniques and procedures to treat intersex abnormalities and with better medical and psychosocial support for patients and their families, the quality of life experienced by individuals who are affected by syndromes of ambiguous genitalia will be further improved.

References and Notes

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