

genetic CLINICS

Newsletter of Indian Academy of Medical Genetics

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Editorial

Indian Academy of Medical Genetics: a new forum for Indian Geneticists

It gives me great pleasure to announce the foundation of the Indian Academy of Medical Genetics (IAMG). The formal inauguration of the IAMG and launching of its official website was held on 27th October 2012 at Manipal, Karnataka. The inaugural program was attended by both the old and new generation of medical geneticists of India as well as by eminent faculty from the USA. The inaugural function was conducted during the Indo-US Symposium on Disorders of the Developing Brain, a conference organized jointly by the Manipal Life Sciences Centre and Kasturba Medical College of Manipal University, Manipal with the support of the Indo-US Science and Technology Forum. This was the first conference to be conducted under the aegis of the IAMG.

The need for such a forum for Indian medical geneticists was perceived for a long time by people in the field. The seeds of medical genetics were sown in India more than four decades ago by pioneers in the field like Dr SS Agarwal, Dr IC Verma, Dr Manorama Thomas and Dr Mrudula Phadke. Over the past decades a few centers have managed to establish state of the art patient care services, establish training programs in Medical Genetics and create awareness about this medical specialty amongst clinical colleagues. The efforts have shown results and during the last decade medical genetics has taken strong roots in India. Thanks to the increasing availability of prenatal diagnosis and DNA based diagnostics, pediatricians and obstetricians are keenly taking interest in the developments in this field. With advances in the use of molecular cytogenetics in cancer diagnosis and prognostication and research on common multifactorial disorders like diabetes mellitus, ischemic heart disease and psychiatric illnesses, no physician can afford to stay away from developments in medical genetics. With increasing recognition of the genetic factors underlying normal development and disease

pathophysiology and with the rapidly increasing clinical applications of medical genetics, it has become pertinent for all the medical fraternity to be aware of advancements in this field.

With the number of medical geneticists in India becoming sizeable, the need was felt to establish a common platform for academic interaction. Formation of the IAMG is the first definitive step towards improving patient care, research and education in the area of medical genetics in India. Our country is vast, the population is very large, the burden of genetic disorders is huge and the number of medical geneticists is still very small. But, we have made a beginning! The task ahead is enormous; especially as the pace of advances in medical genetics is mind boggling, it is impossible to keep oneself up-to-date even in any subspecialty of medical genetics. The IAMG will help members by providing clinically applicable information as well as latest updates on the research front. The website (www.iamg.in) will have sections about useful websites, patient information literature, clinical /diagnostic approaches and upcoming events. The website will also host previous issues of the newsletter GENETICS CLINICS: review articles in these issues are very informative for clinicians and medical students alike. Altogether, the IAMG and its website will provide a forum for interaction for medical geneticists, clinicians and scientists. As the number of medical geneticists is small and will continue to remain too small to cater to the needs of the large population of India, many clinicians can and are trying to update themselves about medical genetics and its application to patient care and research. The IAMG is for all who wish to teach, learn and use medical genetics. It is important for all primary care physicians and all medical specialists to have knowledge of molecular genetics and clinically applicable medical genetics related to their area of work. Without that, the fruits of advancements in

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Office bearers and executive committee members of IAMG with the organizers of the Indo-US symposium on Disorders of the Developing Brain at the IAMG inaugural function in Manipal

medical genetics in India will not reach Indian patients and families with genetic disorders. The IAMG will help to improve genetics teaching in our medical curricula and thereby prepare young medical students for the era of molecular genetics.

I invite all medical geneticists, laboratory geneticists, doctors and scientists interested in medical genetics to visit the IAMG website and send their applications for membership / associate membership of the IAMG. As we usher in this New Year, I thank our readers and contributors and extend my New Year greetings. I hope the IAMG will grow from strength to strength in the coming years.

AS & Phadbee.

Shubha Phadke 1st January, 2013

Announcement

International Conference on Next Revolution in Genetics & Genomics – Applications in Health & Disease

27-29th January, 2013, New Delhi

THEMES

Next generation sequencing, Microarray and their applications, Prenatal diagnosis & Cancer Genetics.

For further information:

Contact Dr I.C.Verma, Dr Ratna Puri, or Dr Sunita Bijarnia at Sir Ganga Ram Hospital, New Delhi. Email: genomics2013@gmail.com | Website: www.genomics2013.com

Clinical Vignette

Single forearm bone on antenatal scan: Diagnosis of VACTERL association on autopsy

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Abstract

Perinatal autopsy remains the standard for determining the cause of a perinatal loss. Despite improvements in prenatal diagnosis, perinatal autopsy remains important in the confirmation and further delineation of prenatal diagnosis. We report here on a fetus spontaneously aborted at 23 weeks of gestation with sonographic detection of a single bone in the forearm. Fetal autopsy aided the diagnosis of VACTERL association.

Introduction

Perinatal death complicates 1.5% of all births.' Such loss is often difficult for the parents and their families to understand and accept. Once a couple has experienced a fetal demise or a neonatal death, they are likely to have serious concerns about the recurrence risk. Some apprehensive women may even be reluctant to undergo another pregnancy till they are sure of strategies to improve future pregnancy outcome.

The most difficult decision for parents is whether to subject the fetus or stillborn to an autopsy. The idea of subjecting the fetus to more "damage/insult" by autopsy is emotionally discomforting. But the responsibility to educate such parents about the advantage of autopsy in revealing more information about the disease and its implications for subsequent pregnancies lies with the caregivers. We are reporting a case where the patient's antenatal ultrasonography suggested skeletal defects but autopsy revealed VACTERL association thus illustrating the utility of fetal autopsy.

Case Report

A 22-years-old primigravida married nonconsanguineously was antenatally diagnosed to have an anomalous fetus with club hand deformity of the left hand and a single bone in the left forearm. She had a spontaneous abortion at 23 weeks of gestation and the fetus was referred for further evaluation.

Fetal autopsy study has the approval of our institutional ethics committee. External examination revealed that the fetus had absent radius with club hand on left side and pedunculated left thumb (Fig 1A & B). On the right side mild hypoplasia of the



Fig 1: Photographs of the fetus showing left radial ray defect and club hand (A), pedunculated left thumb (B)

thumb was noted (Fig 1C). There was hypoplasia of the thenar eminence in both hands. Anal opening was not patent.

On internal examination, left kidney was slightly enlarged and appeared to contain multiple cysts on gross examination (Fig 2). Because of imperforate anus, rectum



Fig1C : Hypoplastic right thumb(C)

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Clinical Vignette



Fig 2: Photographs of the abdominal organs showing normal right kidney, enlarged and multicystic left kidney (A, B).

and anal canal were distended. There were no cardiac and tracheo-esophageal anomalies in the fetus but two-vessel umbilical cord was noted (Fig 3).



umbilical cord.

Radiological studies confirmed the absence of radius with $\overline{Fig 3: Two vessel}$ bowed ulna on left side and

small first metacarpal bone on right side (Fig 4A). Scoliosis of the vertebral column in the lumbosacral region with convexity on left side, and hemivertebrae and fused vertebrae in the lumbosacral region were also noted (Fig 4B & C).



Fig 4: Radiographs of the left upper limb showing absent radius and bowed ulna (A, B), antero-posterior and lateral view radiographs of body showing hemivertebrae and fused vertebrae in the lumbo-sacral region (B, C).

Discussion

All autopsy findings in the fetus suggested that the diagnosis could be VACTERL association. The fetus we report here had vertebral, anal, renal and limb defects along with single umbilical artery. There was no significant adverse antenatal event in the mother. VACTERL stands for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies and limb abnormalities.²³ VACTERL is a non-random association of birth defects related to structures derived from the embryonic

mesoderm. The condition is sporadic and no definite chromosomal abnormality or genetic cause has been identified. It may be associated with trisomy 18 and diabetic mother. The risk of recurrence of the condition is estimated to be very low.

Fetal autopsy in such a situation will be very useful for establishing the diagnosis and for definitive genetic counseling as club hand/single long bone in forearm can also be seen in Fanconi anemia, Holt-Oram syndrome, RAPADILINO and TAR syndrome where the risks of recurrence vary.

In the last five years, tremendous progress has been made in the diagnosis of congenital malformations and diseases. Using high end equipment, detailed ultrasound is been done at an even earlier stage of gestation. Consequently, clinically oriented fetal autopsy has changed to autopsy with known ultrasound findings. A comprehensive diagnosis can be made combining prenatal ultrasound findings, autopsy, radiology and cytogenetic findings.

The perinatal autopsy remains the standard for determining the cause of a perinatal loss.⁴ A fetal autopsy can provide an explanation for a perinatal loss in a significant number of cases often relieving the patient and her physician of blame and guilt. It may reveal a specific disorder for which precise recurrence risk or strategies for prevention are available. In a study by Sankar et al, fetal autopsy was found to provide a definitive diagnosis in 59% of cases with fetal malformations and perinatal deaths.⁵

The diagnosis of a genetic syndrome, which is essential for accurate counseling and pregnancy planning, may depend on revelation of additional findings on autopsy which are not visible even with the most sophisticated sonographic examination. In our case we found additional information which confirmed the diagnosis and helped to provide more evidence-based counseling. Fetal autopsy is a vital part of pregnancy loss management and the high likelihood of obtaining useful information by such an examination makes it well worth the effort.

Clinical Vignette

Acknowledgments

The authors are grateful to the patient and the family for participation in this study. The work was supported by the Indian Council of Medical Research (grant BMS No. 54/5/2010)

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Announcement

Medigencon 2013 & 4th International Rare Disease Day

Medigencon	:	27 th – 28 th February, 2013, organized by Genetic Chapter (IAP) & Maulana Azad Medical College
Rare Disease Day	:	28 th February, 2013, organized by LSD Support Society & Maulana Azad Medical College, New Delhi

For further information, please contact Dr. Seema Kapoor (09968604313) or Dr. Neerja Gupta (09999995630) Email: medigencon@gmail.com

Announcement

Second International conference of the Indian Society for Inborn Errors of Metabolism (ISIEM) (IEMCON-2013)

Conference : $5^{\text{th}} - 7^{\text{th}}$ April, 2013

Workshop : 4th & 8th April, 2013

Organized by : Center of Medical Genetics, Sir Ganga Ram Hospital, New Delhi and ISIEM Highlights : Approach, Diagnosis & Management of IEMs. Newborn screening & Newer advances in metabolic disorders. Renowned faculty from across the world would be participating in the unique meeting designed for all Geneticists, Pediatricians & Neonatologists.

For further information, please contact Dr IC Verma, Dr Ratna Puri or Dr Sunita Bijarnia-Mahay. Email: iemcon2013@gmail.com or visit: http://iemcon2013.com/

Approach to Disorders of Sex Development

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Definition

Disorders of sex development (DSD) are a group of congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical.

- DSD is an umbrella term which encompasses ambiguous genitalia + primary hypogonadism.
- Ambiguous genitalia refers to a congenital defect wherein appearance of the external genitalia is at variance with what is normal for either male or female sex and includes the following: phallus intermediate in size between normal penis & normal clitoris; aberrantly located urethral opening; or at least one impalpable gonad.
- The terms 'intersex', 'sex reversal' and 'hermaphroditism' are considered controversial, derogatory and confusing and are no longer used.

Classification

The new classification of DSD, as per the Lawson Wilkins Pediatric Endocrine Society (LWPES) & European Society for Pediatric Endocrinology (ESPE) 2006, is as follows:

Sex chromosome DSD:

- 45, X (Turner & variants)
- 47, XXY (Klinefelter & variants)
- 45,X/46, XY (Mixed gonadal dysgenesis)
- 46,XX/ 46,XY (& variants causing ovotesticular DSD)

46, XY DSD:

- Disorders of testicular development
- · Disorders of androgen synthesis
- Disorders of androgen action

46, XX DSD:

- Disorders of ovarian development
- Disorders of androgen excess
 - with congenital adrenal hyperplasia
 - without congenital adrenal hyperplasia

Sex Chromosome DSD:

- Numerical sex chromosome abnormality leading to abnormal gonadal development
- Most have gonadal dysgenesis (poorly formed testis: dysgenetic testis; poorly formed ovary: streak gonad)
- Klinefelter and Turner syndromes are the most common sex chromosome DSDs they present with primary hypogonadism
- Sex chromosome DSDs which present with ambiguous genitalia include: 45,X/ 46,XY mixed gonadal dysgenesis & 46,XX/ 46,XY ovotesticular DSD

46, XY DSD:

- Normal male karyotype (46,XY)
- External genitalia: ambiguous or female due to incomplete intrauterine masculinization
- Male gonad(s) are palpable in majority
- Formerly called " male pseudohermaphrodite"

- 46, XY DSD includes:
 - Disorders of gonadal (testicular) development:
 - Complete gonadal dysgenesis (Swyer syndrome)
 - Partial gonadal dysgenesis
 - Testicular regression syndrome
 - Ovotesticular DSD
 - Disorders in androgen biosynthesis & action:

- Androgen biosynthesis defect
- Defect in androgen action
- Leutinizing hormone receptor defect (Leydig cell hypoplasia)
- Disorders of antimullerian hormone & AMH receptor
- Syndromic associations with 46, XY DSD include Frasier syndrome, Denys-Drash syndrome, and Campomelic dysplasia
- Important disorders of androgen biosynthesis are listed in Table 1

Deficiency	Defective synthesis	Phenotype (Autosomal recessive)
17 β hydroxysteroid dehydrogenase	Testosterone deficiency only	DSD
3 β hydroxysteriod dehydrogenase Cholesterol desmolase (P450scc)	Deficiency of testosterone + glucocorticoid + mineralocorticoid	DSD + congenital adrenal hyperplasia + salt loss
17 α hydroxylase (P45017α)	Deficiency of testosterone & excess of glucocorticoid + mineralocorticoid	DSD + congenital adrenal hyperplasia + salt retention + hypertension
P450 oxidoreductase (POR)	Deficiency of testosterone + multisystem anomalies	Antley-Bixler syndrome: DSD + craniosynostosis+ skeletal anomalies + renal anomalies +cognitive deficit
7dehydrocholesterol reductase	Deficiency of testosterone + multisystem anomalies	Smith Lemli Opitz syndrome: DSD + microcephaly + growth retardation + malformations
5 – alpha – reductase	Deficiency of dihydrotestosterone	DSD - variable degree of under- virilization of male external genitalia

Table 1: Disorders of Androgen Biosynthesis

• Disorder of androgen action is the Androgen insensitivity syndrome which is caused by mutations in the AR gene (which encodes the androgen receptor). It can be partial (incomplete masculinization of external genitalia) or complete (female external genitalia), depending on residual activity of the androgen receptor. It has an X-linked inheritance pattern.

• 46, XX DSD:

- Have a normal female karyotype(46,XX)
- Have ambiguous genitalia due to masculinization / virilization of female external genitalia
- Formerly called "female pseudohermaphrodite"
- 46, XX DSD includes:
 - Disorders of ovarian development:
 - Ovotesticular DSD
 - Testicular DSD (SRY+, dup SOX9)
 - Gonadal dysgenesis
 - Conditions with fetal androgen excess:
 - With congenital adrenal hyperplasia
 - 21 hydroxylase deficiency
 - 11 β hydroxylase deficiency

Without congenital adrenal hyperplasia

- Aromatase deficiency
- P450 oxidoreductase deficiency
- Maternal androgen intake/ androgen secreting tumour

• 21-hydroxylase deficiency:

- Most common form of congenital adrenal hyperplasia (>90%) and the second most DSD after mixed gonadal dysgenesis
- Autosomal recessive disorder caused by mutations in the CYP21A2 gene (6p21.3)
- Every newborn with ambiguous genitalia without testes (clinically or on imaging) should be evaluated for 21-hydroxylase deficiency, as it is a potential medical emergency
- Affected females are either virilized at

birth and have ambiguous genitalia or become virilized postnatally and can present with menstrual abnormalities and reduced fertility

- Affected males develop early virilization in childhood i.e. isosexual pseudoprecocious puberty
- Salt-losing crisis occurs in -75% of affected individuals.

Evaluation

Evaluation of an individual affected with DSD should be done in a step-wise manner.

- Detailed history:
 - Growth, development, associated systemic complaints
 - Prenatal history: maternal exposure to androgens/ maternal androgen secreting tumors
 - Detailed family history with at least 3generation pedigree: consanguinity and family history of genital ambiguity, hirsutism, precocious puberty, amenorrhea, infertility, unexplained sudden infant death (due to salt-losing crisis).
 - Androgen insensitivity syndrome (AIS) is an X-linked disorder; males affected with complete AIS may have normal appearing external female genitalia and would be reared as females – therefore, it is important to ask specifically for family history of primary amennorhoea/ infertility in sisters/ maternal aunts/ female cousins on the maternal side.
- Physical examination:
 - Thorough examination of genital anatomy
 - Groin and scrotal/labial folds to be checked for presence of palpable gonads: a

palpable gonad is almost always a testis (or rarely ovotestis); ovaries & streak gonads do not descend and are therefore not palpable

- Phallic size: width & stretched length measurements
- Prader scale: objective scoring of degree of virilization of external genitalia
- Complete general & systemic examination for syndromic associations: anthropometry, dysmorphology evaluation, systemic examination
- Any abnormal virilized /cushingoid appearance of mother
- Medical photography with sensitivity & consent
- Clinical indicators of DSD:
 - Identified in the neonatal period:
 - overt genital ambiguity
 - apparent female genitalia with enlarged clitoris/ posterior labial fusion
 - apparent male genitalia with bilateral undescended testes/ hypospadias/ micropenis
 - discordance between genital appearance & a prenatal karyotype
 - Later presentations in older children/ adolescents:
 - previously unrecognized genital ambiguity
 - inguinal hernia in a girl
 - · delayed or incomplete puberty
 - primary amenorrhea or virilization in a girl
 - breast development in a boy
 - gross or cyclic hematuria in a boy

Investigations

- First-line tests:
 - Cytogenetic analysis
 - · most commonly karyotyping
 - FISH/ MLPA with X- & Y-specific probes can be done for rapid gender assignment in a newborn in select cases
 - differentiates between sex chromosome DSD; 46,XY DSD; & 46, XX DSD
 - Imaging: abdominopelvic ultrasound
 - for identification of Mullerian/ Wolffian structures
 - to detect testes in inguino-scrotal region (not useful for intra-abdominal testes)
 - to rule out possible adrenal anomalies/ associated renal anomalies
- Further evaluation:
 - 46, XY without testes with Mullerian structures:
 - Suggestive of complete gonadal dysgenesis or testicular regression syndrome
 - FISH/ MLPA to look for SRY deletion
 - If syndromic: mutation analysis of SOX9 (campomelic dysplasia) or WT1(Frasier/ Denys-Drash syndrome)
 - If non-syndromic gonadal dysgenesis/ testicular regression: mutation analysis for SRY, NR5A1, DHH, WNT4 genes
 - 46, XY with testes & no Mullerian structures:

Basal testosterone (T) and dihydrotestosterone (DHT) levels to be measured in neonates & post-pubertal individuals. Post hCG stimulation testosterone (T) and dihydrotestosterone (DHT) to be checked in post-neonatal

period & childhood: in normal persons there is a 3 fold elevation of testosterone over baseline, with hCG stimulation.

- Low T level + high FSH/LH=> testosterone biosynthesis defect
- Low T level + high FSH/ LH + low anti Mullerian hormone => gonadal dysgenesis
- Normal testosterone (T), normal or low dihydrotestosterone (DHT), post hCG stimulation high T/ DHT => 5 alpha reductase deficiency => mutation analysis of SRD5A2
- Normal T, normal DHT, normal T/ DHT
 androgen insensitivity syndrome
 mutation analysis of AR
- 46, XX with normal ovaries & normal internal female genital organs:
 - Serum electrolytes for salt losing CAH
 - Serum 17-OH-progesterone: elevated in 21 hydroxylase deficiency CAH
 - Serum 11-deoxycortisol and deoxycorticosterone: elevated in 11βhydroxylase deficiency & reduced in 21hydroxylase deficiency
- For suspected congenital adrenal hyperplasia due to 21-hydroxylase deficiency:
 - Serum electrolyte concentrations / plasma renin assay
 - Karyotype or FISH for X- and Ychromosome detection
 - Measurement of serum concentration of 17-OHP (classic form > 10,000 ng/ dl; nonclassic form: ACTH stimulation may be required to demonstrate increased levels)
 - Measurement of urinary pregnanetriol (increased)
 - Molecular genetic testing of CYP21A2 for confirmation & for prenatal diagnosis for future pregnancies of parents

Management

- Gender assignment:
 - Complex issue with important psychological & social implications
 - Gender should be assigned after the complete diagnostic process
 - Multidisciplinary approach: geneticist, neonatologist, endocrinologist, gynaecologist, psychiatrist, surgeon & social workers
 - Factors influencing gender assignment: diagnosis, genital appearance, fertility potential, therapeutic/surgical options, familial views, cultural biases
- Surgical intervention for gender assignment:
 - controversy about optimal timing of surgery
 - American Academy of Pediatrics guidelines recommend genitoplasty between 2 - 6 months of age
 - Feminizing genitoplasty for infants to be raised as females:
 - removing the corporal bodies/ clitoroplasty
 - creating normal-looking introitus and labia minora & majora
 - vaginoplasty to provide an adequate opening
 - Masculine reconstruction for infants to be reared as males:
 - orchiopexy,
 - · hypospadias repair
 - removal of retained mullerian duct structures
 - Hormone replacement therapy:
 - to induce & sustain puberty
 - to induce secondary sexual

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characteristics & pubertal growth spurt

- to optimize bone mineral accumulation
- for psychosocial maturation
- Boys with hypogonadism:
 - intramuscular injections of testosterone for pubertal changes
 - testosterone gels & patches for virilization of external genitalia
- Girls with hypogonadism:
 - estrogen supplementation to induce secondary sexual changes & for menstruations
 - progestin added after breakthrough bleeding develops or within 1 to 2 years of continuous estrogen
- Management of 21 hydroxylase deficiency:
 - Glucocorticoid replacement therapy has to be given on a regular basis; the dose has to be increased during periods of stress
 - In the salt-wasting form: mineralocorticoid 9αfluorohydrocortisone (fludrocortisone) therapy should also be added
 - Monitoring for symptoms & signs of salt-losing crises to be done & prompt supportive therapy to be initiated
 - Females virilized at birth may require feminizing genitoplasty and/or vaginal dilation
 - Primary prevention of symptoms is possible through newborn screening (17-OHP in heel prick -dried blood spot sample) and early intervention.

Genetic Counseling

- Sex chromosome DSDs:
 - risk of recurrence is not significantly elevated in subsequent pregnancies of the parents of an affected child
 - specific prenatal testing is not required.

- Autosomal recessive disorders:
 - e.g. 21-hydroxylase deficiency, 5-alpha reductase deficiency, Smith-lemli-Opitz syndrome, most disorders of the androgen/ estradiol biosynthesis pathway etc.
 - risk of each subsequent offspring of the affected child's parents getting both the disease-causing mutations is 25%; however, the phenotype may be sex-limited
 - prenatal diagnosis can be done in subsequent pregnancies through targeted mutation analysis in the chorionic villus sample (CVS)/ amniocytes, after identifying the disease-causing mutations in the proband
 - for congenital adrenal hyperplasia due to 21-hydroxylase deficiency, the protocol recommended to minimize the chances of virilisation in the female fetus is given in Figure 1.
- Autosomal dominant disorders:
 - e.g. Frasier syndrome, Denys-Drash syndrome, Campomelic dysplasia etc.
 - in majority of cases, the parents are normal and the disorder occurs because of a de novo mutation in the proband; therefore, the risk of recurrence in subsequent offspring of the parents is not significantly elevated
 - risk of recurrence is 50% if either parent is affected.
 - in some cases there may be gonadal mosaicism in either parent leading to a small risk of recurrence (determined empirically for each disorder) and prenatal testing may be offered for subsequent pregnancies.

• X-linked disorders:

- e.g. androgen insensitivity syndrome
- subsequent male offspring of the parents have a 50% chance of recurrence and prenatal diagnosis can be done through targeted mutation analysis in CVS/ amniocytes after identifying the diseasecausing mutation in the proband.

Figure 1: Prenatal evaluation/management of a pregnancy at risk for 21-hydroxylase deficiency

(Adapted from Nimkarn S and New MI. Horm Res 2006; 67: 53-60)



* Fetal sex not revealed to the family in accordance with the Pre-natal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994

Suggested Reading

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GenEvenT

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The First national conference of the Genetics Chapter of IAP was conducted on 1st – 2nd December 2012 at Raipur. It was held under the auspices of the Genetics Chapter of IAP with the Raipur IAP branch.



Genetics of Preeclampsia

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Preeclampsia (PE) is a potentially life-threatening condition with a multifactorial etiology and a strong genetic contribution. It is associated with significant maternal and fetal morbidity and mortality. It is a hypertensive disorder that occurs in approximately 5% of all pregnancies. Preeclampsia may be of early-onset (symptoms before 34 weeks gestation, type I) or late-onset (symptoms beyond 34 weeks gestation, type II). When preeclampsia occurs within 34 weeks of gestation it shows a clear genetic pattern and contribution of placental risk factors. In late-onset preeclampsia the modulators are primarily factors which regulate the inflammatory process and implantation. Preeclampsia has a polygenic etiology. Environmental factors, gene-gene and geneenvironment interactions all contribute to the causation of the disease. Recently it has been proposed that finer dissection of this disease at the genetic level may help in the development of personalized medicine for more effective PE prophylaxis and therapy.

Evidence of genetic basis

Familial predisposition (2–5 fold increased risk in first-degree relatives of women with PE), Mendelian modes of inheritance (autosomal recessive or autosomal dominant with reduced penetrance) and in some families, involvement of paternal imprinting has been observed for preeclampsia. Various linkage studies have provided evidence for genetic contribution in the occurrence of preeclampsia.' Comparison of the concordance rates in monozygotic and dizygotic twins is one of the techniques used to unravel the contribution of environmental and genetic components to disease susceptibility. One of the largest published twin studies which included 917 pairs of parous monozygotic and 1199 pairs of dizygotic twin sisters

from the Swedish Twin Register and Swedish Medical Birth Register, reported the estimates of heritability of PE to be 0.54 (95% CI=0-0.71), but in case of non-proteinuric gestational hypertension, the heritability estimated was 0.47 (95% CI=0.13-0.61), concluding that paternal genes may play an important role in the development of PE. Records from the Utah Population Database suggested that men who were born of a preeclamptic pregnancy were at increased risk of fathering a pre-eclamptic pregnancy [odds ratio 2.1 (95% CI= 1.0-4.3)], suggesting that susceptibility can be transmitted via paternal genes. The suggestion that preeclampsia may be caused by a paternally imprinted gene (Graves, 1998) is supported by results of studies in mice deficient in p57Kip2, which is a paternally imprinted gene in both humans and mice (i.e. it is only expressed from the maternally derived chromosome).^{2,3} Figure 1 illustrates the mechanism of paternal imprinting. A decrease in expression of p57Kip2 has been associated with abnormal proliferation of trophoblast cells, which may be relevant to pre-eclampsia. Female mice heterozygous for p57Kip2 gene that were mated with heterozygous males showed signs of preeclampsia, including hypertension, proteinuria and increased endothelin levels in late pregnancy. These features were also noted in heterozygous females which were mated with wild-type males, but not in wild-type females mated with either heterozygous or wild-type males, i.e. symptoms were only seen in females carrying p57Kip2-deficient pups regardless of their own p57Kip2-expression status. This indicates that the fetal genotype may play a role in the development of pre-eclampsia. The results of animal models reveal that symptoms similar to those exhibited by women with preeclampsia can be initiated either by maternal factors (IGFBP-1 mice), by factors originating in the fetus (p57Kip2 mice) or

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Figure1. Example of paternal imprinting of gene A in PE. The red cross indicates imprinting of 'A' allele in paternal gene. 'a' denotes mutant allele. Fetal expression of maternal allele A is required for a normal pregnancy. If the mutant maternal allele is transmitted to the fetus, loss of gene function results, as the wild-type paternally inherited allele is not expressed, resulting in preeclamptic pregnancy.

by an interaction of both maternal and fetal factors (renin /angiotensinogen). If the same holds true for humans, with patterns of genetic influences differing between pedigrees, this will complicate the analysis of the underlying genetics of the disorder further.

Another possible genetic basis which has been considered is a mitochondrial mode of inheritance. However, epidemiological data indicates that mitochondrial genes do not contribute to the inheritance of PE in majority of the families.

Candidate genes

The easiest method to identify genetic association is to compare the frequency of genetic variants in cases and controls. Many researchers have investigated single nucleotide polymorphisms (SNPs) in one or more genes. Although studies of over 70 candidate genes have been reported, only eight genes account for 70% of published research into candidate genes for PE. Genes involved in hemodynamic disturbances (renin, angiotensinogen, angiotensin-converting enzyme and angiotensin receptors); inherited thrombophilias (coagulation factor V Leiden variant, prothrombin and methylene tetrahydrofolate reductase); the NOS3 gene regulating the synthesis of the vasorelaxant eNOS (endothelial nitric oxide synthase); genes encoding (tumour necrosis factor- α , IL-6) and cytokines oxidative stress (xantine oxidase and superoxide dismutase) are amongst the most common genes studied through candidate gene association studies.⁴ Table 1 lists some examples of candidate gene studies in pre-eclampsia. All these candidate gene studies support the idea that PE has a heterogeneous basis with variations between different ethnic groups.

Genome Wide Association Studies (GWAS)

Genome-wide screening is an unbiased approach providing novel insights into the disease process. However, the lack of a recognizable phenotype in men or nulliparous women, and uncertainty of the mode of inheritance in PE, has made it difficult to carry out conventional linkage analysis. Genomewide linkage screening (GWLS) has been carried out using affected sib-pair analysis, revealing significant linkage on chromosomes 2p13, 2p25 and 9p13, and suggestive linkage on 2q, 9p, 10q, 11q and 22q chromosomes. However, other studies were unable to replicate these results. GWAS conducted in Icelandic, Australian, New Zealand and Finnish families indicated possible susceptibility loci for PE on chromosome 2p13, stating the influence of PREG1 gene in conferring risk to PE. Recently a study reported a significant association of a novel SNP on chromosome 2q14.² close to the Inhibin beta B (INHBB) gene. However, on gene expression and bioinformatic analysis, functional importance was found to be low. Another study aimed to identify maternal SNPs and copy-number variants (CNVs) involved in the etiology of PE. Out of three rare but recurrent deletions, a functionally important copy-number deletion in the PSG11 gene was discovered through genome-wide CNV analysis.7 Furthermore, larger replication studies are needed to ascertain the role of these susceptible loci in PE.

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Table 1.	Some	of the	candidate	σene	studies	in	PF 4,5	i,6
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Gene	Function	SNP	Population	References	Association
ERAP1 & 2	Antigen presentation	rs2549782 rs17408150	Australian New Zealand Norwegian	Johnson et al. , 2009	Yes
		rs2549782 rs17408150	African American	Hill et al. , 2011	Yes
		rs2549782 rs17408150	Chilean		No
TNFSF13B	Regulation of immune response to infections, autoimmune disease. and	rs16972194 rs16972197 rs56124946	Australian New Zealand	Fenstand et al., 2010	Yes
	inflammation		Norwegian		No
HLA	Immunosuppressive properties	G*0106 HLA-G		Moreau et al., 2008	Yes
VEGF	Expressed in lymphatic endothelial cells and	rs1485766 rs6838834	African American	Srinivas et al, 2010	Yes
	participatesin mitosis, migration, differentiation, and survival cells	rs7664413	Caucasian	Srinivas et al, 2010	Yes
		rs2010963	Hungarian	Banyasz et al, 2006	No
		rs2010963	Mexican	Garza-Veloz, 2011	No
eNOS	Regulation of smooth muscle tone in the	894G>T	Colombian	Serrano et al, 2004	Yes
	vascular system		Japanese	Kobashi et al, 2001	Yes
		4b/a rs1799983 rs2070744	Caucasian	Zdoukopoulos et al, 2011	No
CYP11B2	Synthesizing the mineralocorticoid aldosterone	-344 C/T		Escher et al, 2009	No
SERPINE1	Endothelial plasminogen activator inhibitor-1 (PAI-1),	4G/5G		Yamada et al, 2000	Yes
	the major inhibitor of fibrinolysis			Mutze et al, 2008	No

 Image: Clinics 2013, Volume 6, Issue 1

Conclusion

PE is a common disease in pregnancy worldwide, where maternal and fetal factors result in a multicomponent risk. Till now, no single factor has been identified as capable of determining the disease. As described earlier, many candidate gene studies in different populations have identified various SNPs to be associated with PE. However, these findings will need to be validated by currently available genome-wide approaches. Furthermore, multicentric studies are necessary to determine the prognostic effect of identified markers. In spite of considerable advances in comprehending the PE pathogenesis, the development of simple tests to identify individuals or populations at risk still remains a challenge, epidemiologically and clinically.

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Emerging Concepts in Diagnostics and Therapeutics

Contributed by : Dr Shagun Aggarwal. Email: shagun.genetics@gmail.com

Pompe disease always in the news - emerging data & newer strategies¹

Prater et al report the long term outcome in 11 patients successfully treated with enzyme replacement therapy (ERT) with alglucosidase alfa for infantile Pompe disease. The patients were recruited if they were ventilator free, had ERT institution before 6 months age and remained alive beyond 5 years age. The mean age of outcome assessment was 8 years. All patients were CRIM (cross-reactive immunologic material) positive and remained independent of invasive ventilation. Seven were ambulant, while four required assistive ambulatory devices. All had sustained improvement in cardiac parameters. Residual muscle weakness, hearing loss, risk for arrhythmias, hypernasal speech, dysphagia with risk for aspiration, and osteopenia were the problems reported. There are two reports of successful immune tolerance induction in CRIM negative individuals receiving

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ERT and having clinical deterioration due to development of antibodies against the enzyme.^{2,3} The authors have used immunomodulatory drugs like rituximab, methotrexate, gamma globulins and a novel anticancer drug Bortezomib. The authors using bortezomib reported a decline of antibody titres in the tune of 2,048-fold in one patient and 64fold in two patients with concomitant sustained clinical improvement. They conclude that the addition of bortezomib to immunomodulatory regimens is an effective and safe treatment strategy in infantile Pompe disease, with potentially broader clinical implications for other diseases requiring protein replacement therapies.

Medical Genetics and Telemedicine - the Happy $\mathsf{Twosome}^4$

The use of telemedicine for providing medical services to remotely located patients has been in use for many fields of medicine. Teleconferencing has also been useful for geneticists in exchanging rare case findings. Hilgart et al from UK report a review of an application called "Telegenetics" which is the use of telemedicine services for providing clinical genetic services to patients. They have concluded their findings from 14 literature reports, albeit all are limited by their small size and lack of statistical analysis. The authors state that Telegenetics is useful for patient counseling and evaluation of suspected pediatric genetic disorders. They found a high level of patient satisfaction and receptivity in all reports. However, they conclude that the service needs to be evaluated for accuracy of diagnosis and impact on eventual outcome, before any conclusions about its routine utility can be made.

The art of story-telling- narrative medicine in clinical genetics⁵

Nowaczyk MJM writes beautifully about narrative medicine, defined as "medicine practiced with the narrative competence to recognize, absorb, interpret and be moved by the stories of illness" or more simply "a medicine practiced by someone who

knows what to do with stories". The article outlines how clinical genetics practice already encompasses the art of storytelling by the patients with the various narrative plots- restitution, chaos, quest & illness-as-normality and the art of story-listening by the doctors with the attendant skills of attention, representation & affiliation. The author writes about the therapeutic effects of this process for the doctors as well as patients & care-givers, its impact on finding purpose & meaning in life in the face of incurable diseases and its insight provoking effects. The article also tells how being conversant with varied genres of literature, a skill to read others' non-verbal cues and above all a compassionate heart can help a geneticist to practice narrative medicine or write a story of his/her own.

Exome sequencing for the unborn⁶

Shamseldin et al report the application of exome sequencing and autozygome analysis in identifying the mutated gene in a family suffering from recurrent in utero fetal demise. They found a novel mutation in the CHRNA1 gene which is known to be causative for fetal akinesia and multiple pterygium syndrome. The authors propose that their report should inspire a systematic examination of the extent of "unborn" Mendelian phenotypes in humans using next-generation sequencing technology.

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PhotoQuiz

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Contributed by: Dr Shubha R Phadke, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow Email-shubharaophadke@gmail.com

Identify this condition with intellectual disability, short stature and typical dysmorphic features.



Answer to PhotoQuiz 18 of the previous issue **Proteus Syndrome (OMIM #176920)**

Proteus syndrome is an uncommon syndrome with an incidence of <1 case per 1 million population. The clinical manifestations are protean and consist of patchy or segmental asymmetric overgrowth and hyperplasia of multiple tissues and organs, along with susceptibility to the development of tumors. The types of skin lesions include linear verrucous epidermal nevi, intradermal nevi, shagreen patches, haemangiomas, lipomas, macrodactyly and syndactyly, and varicosities. Craniofacial anomalies include hydrocephalus, macrocephaly, facial and ocular asymmetry, retinal detachment, scleral tumours, prognathism, malocclusion and hyperostoses. There may be a characteristic warty, hyperplastic plantar overgrowth that has been termed a 'moccasin lesion'. Recently, through exome sequencing, the oncogene AKT1 has been found to be involved in the etiology of Proteus syndrome.



geneti

- Divya P, Vellore
- Gireesh S, Kozhikkode
- Beena Suresh, Chennai
- Aruna G, Bangalore

Correct responses were given by:

- Rajni Khajuria, New Delhi
- Prashant Kumar Verma, email
- Saminathan D, Trichy
- Ravi Goyal, Kota
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