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گۆڤاری زانکۆی سلێمانی نەپریلی ٢٠٠٤ بەرگ ٧ (١) بەشی A لاپەرە (٩٥-١٠٣)

Azoospermia in Sulaimani

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Abstracts
One hundred patients with azoospermia were diagnosed, investigated and treated accordingly, this is a prospective study carried on patients presented with infertility, abnormal genitalia, accidental azoospermia, from July 2001 to June 2002.
***Design;** clinical diagnosis was made by history, physical examination, and serial seminal fluid examination, testicular biopsy examined by consultant pathologist and hormonal assay.**Objective;** to identify the etiology of the azoospermia and to determine their future outcome.**Results;** azoospermia regarded as one of the difficult condition for the treatment as most of the cases are due to primary testicular failure . **Conclusion;** small testis with high FSH need no farther assessment better to explain the condition for them .*

Keywords; Seminal fluid analysis , Azoospermia , Oligospermia, Infertility , Hypogonadism, Gonadotropin.

Introduction

Azoospermia has been reported in the range of 10 to 20% of cases.[1] azoospermia has been associated with a number of genetic risk factors such as constitutive chromosome abnormalities, microdeletions of the Y chromosome (AZF region) and mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[2] Cytogenetic and molecular studies of azoospermic and oligozoospermic males have suggested the presence of azoospermia factors (AZF) in the human Y chromosome. Deletion in three Y chromosomal regions AZFa, AZFb and AZFc has been reported to disrupt spermatogenesis and cause infertility.[3] Microdeletions within the azoospermia factor region (AZF) are often associated with azoospermia and severe oligospermia in men with idiopathic infertility. [4] Microdeletions of the long arm of the Y chromosome (Yq) were described in men with idiopathic azoo- or oligozoospermia and seem to cause impairment of spermatogenesis. Deletion frequencies differ considerably among selected infertile men.[5] Y chromosome microdeletions in the azoospermia factor (AZF) locus have been associated with spermatogenic failure. The frequency of AZF deletions is estimated to be about 10-18% in subgroups of idiopathic azoospermia and severe oligospermia, whereas the deletion frequency is estimated to be about 1.5-10.6% in the general population.[6] The DAZ (deleted in azoospermia) gene family on the Y chromosome long arm is the major candidate for the AZFc (azoospermia factor c)

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oligospermia.[8].

Men with Y chromosome long arm deletions, resulting in infertility, form a very significant group of patients, with a view to treatment. With recent advances in assisted reproductive techniques, it is expected that if these patients undergo intracytoplasmic sperm injection, their male offspring will inherit the same deleted regions of Y chromosomes. Hence,characterization of these deleted Y regions provides information , allowing patients to make informed decisions about reproduction.(9)The murine autosomal deleted in azoospermia-like protein (mDAZL) is a germ cell-restricted RNA-binding protein essential for sperm production. Homozygous disruption of the mDAZL gene results in the absence of germ cells beyond the spermatogonial stage.. Understanding how mDAZL regulates the target mRNAs will provide new insights into spermatogenesis, strategies for therapeutic intervention in azoospermic patients, and novel approaches for male contraception.[10]Spermatogenic dysfunction may result from thickening of seminiferous tubular basement membrane (BM) with tubular sclerosis.[11

Inhibin B controls FSH secretion , but it is not known in which way germ cells contribute to inhibin B production. The regulation of inhibin B production changes during life. There is a clear inverse relationship between serum inhibin B and FSH in the adult. Serum inhibin B levels are strongly positively correlated with testicular volume and sperm counts. In infertile patients, inhibin B decreases and FSH increases. In general, there is very good correlation with the degree of spermatogenetic damage, with the arrest at the earlier stages having the lowest inhibin B levels. However, for unknown reasons, there are cases of Sertoli- cell- only syndrome with normal inhibin B levels. Inhibin B and FSH together are a more sensitive and specific marker for spermatogenesis than either one alone In summary, inhibin B is a valuable index of spermatogenesis [12] but serum inhibin B level seems to be more accurate than serum FSH level in prediction of the presence of testicular spermatozoa in patients with nonobstructive azoospermia.[13].

Undescended testis may cause male infertility and Impaired spermatogenesis was observed as early as age 4 weeks. Germ cell apoptosis was significantly more frequent on the affected side in all age groups with the most prominent incidence at age 6 weeks.[14]

An increasing chemical and physical agents in the environment, introduced and spread by human activity, may affect male fertility .

Men exposed to pesticides had higher serum oestradiol concentrations, and that men exposed to solvents had lower LH concentrations than non-exposed men. All of these effects were greater in men with primary infertility than in men with secondary infertility. this may worsen the effects of pre-existing genetic or medical risk factors. [15] With the advent of assisted reproductive technology , testicular biopsy is now used therapeutically to retrieve sperm for intracytoplasmic sperm injection (ICSI)

In the testes where no spermatozoa were found on biopsy, the rate of X-Y bivalent indicated the presence of spermatozoa in the opposite side. Thus, it may be concluded that the rate of X-Y bivalent formation in spermatocytes may predict the presence and amount of spermatozoa in the testicular tissue of

azoospermic men. [17] Testicular volume, testosterone levels, and results of the hCG test are important predictive factors of spermatogenesis.[18]

With the advent of intracytoplasmic injection, the management of azoospermia has become ever more important. Gametic manipulation to produce biological offspring is not feasible unless sperm from the azoospermic male patient is obtainable. [19] Sperm for ICSI is relatively difficult, but it is a practical method to provide fertility for obstructive or non-obstructive azoospermia men. Its efficacy, however, is needed to be improved.[20]

Patients and ,methods

After diagnosis of azoospermia , determined by 3 seminal fluid analysis, patients were asked about the history , appearance of secondary sexual character , including married period and previous fertility , surgical and medical illness , drugs ; name , duration of its intake, trauma to the genitalia, previous visits for treatment of the azoospermia ; results and the therapy he received or any surgical intervention he had .Generally asked about their residence, occupational hazard he had like exposure to heat, radiation, chemical, smoking, alcohol and any other toxic substances he had. General physical examination for their body built , development of the secondary sexual character , gyncomastia , examination of the genitalia , development of the scrotum, presence of the testis, their size and site .palpation of the neck of the scrotum for presence or absence of the vas deferens , looking for varicocele , hydrocele and scar of previous surgery or site of trauma. A rectal examination to determine the prostate gland. Each of these findings were identified and recorded. Then the patients had ultrasonic examination of his testis, skull X- ray for his sella-tursica, hormonal assessment for F.S.H., L.H. In those who were deficient secondary sexual character serum testosterone also measured.

Testicular biopsy performed for them and the results were recorded.

Results

The medical records of azoospermic patients who were evaluated and treated , were prospectively analyzed for history, physical examination findings, endocrine profiles, testicular histology and sperm retrieval rates. Based on these parameters, cases were placed into diagnostic categories that included obstructive or non-obstructive azoospermia.

one hundred patients with mean age of 36 year were founded to have azoospermia, 18 were obstructive and 82 non-obstructive .Hormonal study showed ;LH normal in 57, high in43, FSH; normal in 23 , high in 77, 23 normal FSH occur with normal LH , no rising LH with normal FSH founded, testosterone low in 1(table-1). Vasal agenesis;7, 6 had vasoepididemostomy, 1 had 20 million sperm after 6 month from the surgery. Secondary sexual character undeveloped in 3, Married ;72.

Discussion

The study shows most of the patients were from sulaimani which has the greatest population ,

The worker including those with heavy duty and building worker, the solder and the then the farmer, may be due to the rat of the distribution of the businesses and the marital status ability.

Malaria , typhoid and chemical exposure identified in 9 patients, rantiden for 1 year and tagamet for 2 months was the drugs which were used by 2 patients and is known to affect the spermatogenesis. Herniotomy in 2 patients, which may reflect it as a common surgical proplem.

Bilateral small testis less than 2 cm in 37 patients which mean 37% testiculer growth failure.

FSH high in 77 patients which mean 77% activation of the gonadal–hypothalamic-pituitary axis , with secondary hormonal testicular stimulation to form sperm. LH is high in 43 patients which reflect testicular stimulation for androgen production although 1 patient with low testosterone were identified . No low FSH or LH were identified , this mean there was no hypothalamic or pituitary cause . Isolated gonadotropin RH deficiency ,although it is uncommen, it is a second to klineflters syndrome as a cause of hypogonadism. Isolated LH and isolated FSH deficiency is another cause of hypogonadism and azoospermia.[21]

From January 1993 through February 2000 , 331 patients were reviewed at the clinic of Reproductive Biology of the Hospital Juarez de Mexico , SSA, 66 patients were found with azoospermia (19.93%). Studies performed were: seminogram, testicular and transrectal ultrasonography, kariotype, deferentovesiculography and testicular biopsy. Radioimmunoassay of gonadotropins (FSH, LH) and testosterone was also practiced. They founded the cause of azoospermia was: secretory (85.19%) of which 41.3 % was idiopathic, 10.9% had germ cells aplasia, 10.9% varicocele, 10.9% Klinefelter syndrome. Secondary secreting azoospermia was found in two cases with Kallman's syndrome one patient had excretory and 7 obstructive azoospermia. They concluded that azoospermia was diagnosed in 19.93% with a mean age of 30 years. 85.19% had primary secretary azoospermia with FSH & LH hypergonadotropism in 85.8 and 56.4% respectively Obstructive azoospermia was seen in 12.96% and only one case (1.85%) presented excretory azoospermia[1]

Ravnik *et. al.* screened 80 men with idiopathic azoospermia, 50 men with oligozoospermia, 70 men with oligoasthenoteratozoospermia, and 7 men with congenital bilateral absence of the vas deferens (CBAVD), as well as 95 controls from Slovenia, for mutations in 10 CFTR exons that include the majority of the most common cystic fibrosis (CF) disease causing mutations, also to evaluate the risk for CF in children born after the intracytoplasmic sperm injection method of in vitro fertilization (IVF). No tested individual had mutations in both CFTR alleles. Altogether 13 different nucleotide alterations were identified. The frequencies of both CFTR gene alterations and polymorphism's did no t differ significantly between the control group and men with idiopathic non-obstructive azoospermia and sub-fertility, but were significantly increased in men with CBAVD. Their results suggest that CFTR mutations are not associated with errors in spermatogenesis and nonobstructive pathology of urogenital tract in men with any frequency. However, genetic counseling and CFTR mutation screening continue to be recommended for men with obstructive azoospermic conditions and their female partners.[22]

Table-1-Occupation

Worker 35	Student 4	Carpenter 2	Mechanic 1	Coordinator 1
Solder 19	Teacher 4	Shoemaker 2	Security 1	
Farmer 17	Shopkeeper 3	Tailor 1	Free 1	
Clerk 5	Driver 2	Welding 1	Butcher 1	

Table-2-Drugs history

Rantidin for one year 1	Tagamet for 2 month 1	Anticonvulsant(rivolin, espilot) 1

Table –3-Medical illness

Malaria 3	Chemical exposure 3	Mumps 1	Impotence with low libido 1
Typhoid 3	Hepatitis 1	Brucellosis 1	Syphilis 1

Table-4- Surgical history

Herniotomy 2	UTI 1	bullet to testis followed by right testicular orchiectomy 1	Testicular abscess drainage 1	Renal stone surgery 2
Laprotomy 1	Pile with testicular trauma 1	Nephrectomy 1	Prostatectomy 1	Varicocelectomy 1

Table-5-Testiculat size (more than 4cm.long axis is normal, less than 2cm. is small)

Bilateral small 37	Right small only 3	Left small only 1	Left large 1
Bilateral absent 1	Right absent only 1	Left undescended only 1	Normal testis 55

Table-6- Hormonal assessment

HORMONE	HIGH	LOW	NORMAL
LH	43		57
FSH	77		23
TESTOSTERONE		1	

Table –7Testicular biopsy

Complete spermatogenic arrest 59	TB 5	Germ cell hypoplesia 2	Normal in 13
Partial or incomplete spermatogenic arrest 7	Sertoli cell only 6	Leydig cell hypoplesia 7	No testis inside the scrotum 1

Because a pregnancy can be achieved with out a male infertility evaluation , some have questioned its usefulness. However, by bypassing a urological evaluation the man might not learn the cause of infertility and not be offered specific corrective therapy. In addition, men with sub fertility may have a serious underlying medical problem that could also be over looked. We determine the incidence of significant medical pathology discovered during a male infertility evaluation (5 patients had TB epididimities). Klottis PN *et. al* . founded Significant medical pathology was discovered in 33 of 536 (6%) patients. A total of 27 patients had genetic abnormalities, including cystic fibrosis mutations in 24 and karyotypic abnormalities in 3. Of the remaining 6 patients 1 had testis cancer , 1 prostate cancer , 3 diabetes mellitus and 1 hypothyroidism. [23]

Schoor RA *et. al.* In their study of a total of 153 azoospermic men .He founded men with obstructive azoospermia 96% had follicle-stimulating hormone (FSH) 7.6 mIU/ml. or less, or testicular long axis greater than 4.6 cm. Conversely , 89 % of men with non - obstructive azoospermia had FSH greater than 7.6 mIU /ml., or testicular long axis 4.6 cm. or less.[24]

In our study we did 6 vasoepididymostomy, only 1 shows sperms in his seminal fluid, the others had failed , Tsujimura *et. al.* Showed the efficacy of re-anastamosis in 30 patients with obstructive azoospermia , including 19 postvasectomy cases; 7 cases complicating inguinal herniorrhaphy; 2 cases with a characterized isolated congenital anomaly ; 1 case of Young's syndrome; and 1 case with an unknown, possibly congenital cause. In the postvasectomy group, successful vaso-vasostomy was achieved in 15 of 18 cases (83.3%). Duration of obstruction in the 3 cases where anastomosis failed was 6, 9, and 20 years. In the group where obstruction followed inguinal herniorrhaphy, unilateral vaso-vasostomy was performed in 6 cases , and transepididymovasostomy was performed in 1 case . Success was achieved in 3 of 6 cases (50%). In all 4 remaining cases , epididymovasostomy or transepididymovasostomy was performed, but success was achieved only in the case of Young's syndrome. Natural pregnancy occurs in only 4 affected couples, postoperative sperm counts were relatively satisfactory as in previous reports.[25]

Conclusion

In the vast majority of patients obstructive azoospermia may be distinguished clinically from non-obstructive azoospermia with a thorough analysis of diagnostic parameters. Based on this result, we believe that the isolated diagnostic testicular biopsy is rarely if ever indicated. Men with high FSH more than 15 mIU/ml or testicular long axis 2 cm. or less may be considered to have non-obstructive azoospermia and counseled accordingly. These men are best treated with therapeutic testicular biopsy and sperm extraction, with processing and cryopreservation for usage in in vitro fertilization and intra-cytoplasmic sperm injection if they accept advanced reproductive treatment. Diagnostic biopsy is of no other value in this group . Men with normal FSH 2-15 mIU/ml, testicular long axis greater than

2 cm. may elect to undergo reconstructive surgery with or without testicular biopsy and sperm extraction, or testicular biopsy and sperm extraction alone depending on their reproductive goals.

References

(1)Hernandez Uribe L, Hernandez Marin I, Cervera-Aguilar R, Ayala AR. Frequency and etiology of azoospermia in the study of infertile couples *Ginecol Obstet Mex* 2001Aug;**69**:322-6

(2)Halley DJ, Van Hemel JO, van den Ouwel AM, Pieters MH, Weber RF, Govaerts LC. Genetic risk factors in infertile men with severe oligozoospermia and azoospermia. Dohle GR, *Hum Reprod* 2002 Jan;17(**1**):13-6

(3)Sawai H, Komori S, Koyama K. Molecular analysis of the Y chromosome AZFc region in Japanese infertile males with spermatogenic defects. *J Reprod Immunol* 2002 Jan;53(**1-2**):37-44

(4)Tunca Y, Martens PR, Wilroy RS, Tharapel AT. Deletion of RBM and DAZ in azoospermia: evaluation by PRINS.Kadandale JS, Wachtel SS, *: Am J Med Genet* 2002 Jan 15;107(**2**):105-8

(5)Tzschach A, Thamm B, Imthurn B, Weber W, AlexanderH, Glander HJ, Froster U; Absence of Yq microdeletions in infertile men. *Arch Androl* 2001 Nov-Dec; 47(**3**) :167 -71

(6)Ioulianos A, Sismani C, Fourouclas N, Patroclou T, Sergiou C, Patsalis ; A nation - based population screening for azoospermia factor deletions in Greek-Cypriot patients with severe spermatogenic failure and normal fertile controls, using a specific study and experimental design. PC.: *Int J Androl* 2002 Jun;25(**3**):153-8

(7)Foresta C, Bettella A, Moro E, Rossato M, Merico M, Garolla A, Ferlin A. Inhibin B plasma concentrations in infertile patients with DAZ gene deletions treated with FSH.: *Eur J Endocrinol* 2002 Jun;146(*6*):801-6

(8)Ewis AA, Lee J, Shinka T, Nakahori Y Microdeletions of a Y-specific marker, Yfm1, and implications for a role in spermatogenesis. *J Hum Genet* 2002;47(**5**):257-61

(9)Gole LA, Ng SC.- FISH analysis of Y chromosome long arm deletions in subfertile men considering ICSI. A report of two cases. *J Repored Med* 2002 Jun;47(**6**):515-8

(10)Jiao X, Trifillis P, Kiledjian M. Identification of target messenger RNA substrates for the murine deleted in azoospermia-like RNA-binding protein. *Biol Reprod* 2002 Feb;66(**2**):475-85

(11)Fujisawa M, Dobashi M, Yamazaki T, Okada H, Kamidono S. Distribution of intracellular and extracellular expression of transforming growth factor-&bgr1 (TGF-&bgr1) in human testis and their association with spermatogenesis.,*Asian J Androl* 2002 Jun;4(**2**):105-9

(12)Meachem SJ , Nieschlag E, Simoni M Inhibin B in male reproduction: pathophysiology and clinical relevance.; *Eur J Endocrinol* 2001 Nov;145(**5**):561-71

pathophysiology and clinical relevance.; *Eur J Endocrinol* 2001 Nov;145(**5**):561-71
[13]Brugo-Olmedo S, De Vincentiis S, Calamera JC, Urrutia F, Nodar F , Acosta AA.Serum inhibin B may be a reliable marker of the presence of testicular spermatozoa in patients with nonobstructive azoospermia. *Fertil Steril* 2001;**76**(6):1124-9.
[14]Tomomasa H, Adachi Y, Oshio S, Umeda T, Irie H, Ishikawa H. Germ cell apoptosis in undescended testis: the origin of its impaired spermatogenesis in the TS inbred rat. *J Urol* 2002;**168**(1):343-7.
[15]Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. *Hum Reprod* 2001;**16**(8):1768-76
[16]Chan PT, Schlegel PN.: Diagnostic and therapeutic testis biopsy. *Curr Urol* Rep 2000;**1**(4):266-72.
[17]Yogev L, Gamzu R, Paz G, Kleiman S, Botchan A, Hauser R, Yavetz H.: Rate of homologous chromosome bivalents in spermatocytes may predict completion of spermatogenesis in azoospermic men. *Hum Genet* 2002;**110**(1):30-5 .
[18]Madgar I, Dor J, Weissenberg R, Raviv G, Menashe Y, Levron J.: Prognostic value of the clinical and laboratory evaluation in patients with nonmosaic Klinefelter syndrome who are receiving assisted reproductive therapy. *Fertil Steril* 2002 Jun;**77**(6):1167-9
[19]Lin WW. Diagnosis and treatment of the azoospermic patient. *Curr Urol Rep* 2001; 2(6):448-52.
[20]Li M, Zhuang G, Zhou C: Using testicular sperm to provide fertility for azoospermia men *Zhonghua Yi Xue Za Zhi* 2000;**80**(8):588-90
[21]Emil A. Tanagho. Jack W.Mc Aninch. Smiths General Urology , 14 edition, 2000, A Lang medical book, philadlphia. ,757.
[22]Ravnik-Glavac M, Svetina N, Zorn B, Peterlin B, Glavac D. Involvement of CFTR gene alterations in obstructive and nonobstructive infertility in men.*Genet Test* 2001;**5**(3):243-7.
[23]Kolettis PN, Sabanegh ES Significant medical pathology discovered during a male infertility evaluation.: *J Urol* 2001;**166**(1):178-80
[24]Elhanbly S, Niederberger CS, Ross LS The role of testicular biopsy in the modern management of male infertility. Schoor RA, : *J Urol* 2002];**167**(1):197-200.
[25]Tsujimura A, Matsumiya K, Koga M, Miura H, Nishimura K, Kitamura M, Kondoh N, Takeyama M, Takahara S, Okuyama A.: Outcome of surgical treatment for obstructive azoospermia. *Arch Androl* 2002 Jan-Feb;**48**(1):29-36.

بێ تووی

ئاسۆ عمر ڕەشید و سەباح عابد
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پوختە

لیکولینە وە یە کی دە سبیکی یە ، لە سە ر سە د نە خوش لە نە خوشخا نە کانی سلیمانی فیرکاری و چواربا خی فیرکاری لە نیوان مانگی تموزی ٢٠٠١-تاکو مانگی حوزە یرانی ٢٠٠٢ نە نجامدراوە .

ئەم نەخوشانە سکالای (نە زووکی، شیواوی کوئە ندامی زاوزێی دە ڕە کی و بی تووی) یان هە بوو .

باش ڕابرسی وێەکالاکردنی وهی میژووی نەخوشیی کە و بە وردی پشکنینی نە خوشە کان نیردران بو چە ند جار بشکنینی تووا و، هورمون و نموونە ی شانەیی لە باتوویان وە ڕگیرا. ئەمەش هەمووی تابزانین هوی (بی تووی) یە کە جی یە و نە توانریت جیان بو بکریت.

بیتووی باریکی ناساغی سە خته جارە سە ری کرانە جونکە هوی زوربە ی بارە کان نازانریت.

لە دە ڕنە نجامدا دە ڕکەوت ئەو نەخوشانە ی باتوویان بووکاوەتەوە و ناستی هورمونی توخکلدانوجکە هورمونی هەژێنە ری (FSH) یان بەرزە بیویستیان بە بشکنینی تر نییە و نە بیت بیهیوایی بارە کە یان تیبکە یە نریت.

سائل منوي بدون حيامن

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الخلاصة

اجريت هذه الدراسه على ١٠٠مرضى كانو مصابين بانعدام الحيامن في سائلهم المنوى ، خلال شهر تموز من عام ٢٠٠١-ولغاية شهر حوزيران ٢٠٠٢ ، فى مستشفيات السليمانيه التعليمي و جوارباخ التعليمى.

بعد المسائله التاريخيه للمرض واجراء الفحوصات للسائل المنوى والهورمنىواخذ النمادج النسيجيه من الخصيتين تم مراجعة البيانات لايضاح اسباب المرض.

تبين من النتائج التى حصلنا عليها ان المرضى الدين لديهم خصيات صغيرة وهورمونات (FSH) عالية لا يحتاجون الى اجراء الكشوفات النسيجية والعلاج بل ايضاح المرض لهم .

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