Possible Relationship Between Infertility and Alkaptonuria

Mehmet Vural[1], Hakan Buyukhatipoglu[2], Ahmet Demirkol[3], Murat Uludag[3]

Harran University, School of Medicine, Departments of Obstetrics and Gynecology[1], Internal Medicine[2] and Physical Medicine and Rehabilitation[3], Şanlıurfa, Turkey

Eur J Gen Med 2010;7(4):447-449

Received: 25.05.2010

Accepted: 08.06.2010

***Correspondence**: Dr. Mehmet Vural, Department of Obstetrics and Gynecology, School of Medicine, Harran University, 63300, Sanliurfa, Turkey*
Tel: 9041434183000, Fax: 904143183192
E-mail: drmvural@yahoo.com

ABSTRACT

Alkaptonuria is a rare metabolic disease which is not known to cause infertility up to now. Reported manifestations are mainly darkening of urine, ochronotic pigmentation of skin and various musculoskeletal symptoms. We aimed to report a family having many members affected with alkaptonuria and infertility. For the couple first we met from this family, after diagnosis of alkaptonuria, noticed them to have infertility. Infertility test including hysterosalpingography and sperm analysis are performed. After detailed investigation we noticed coexistence of infertility and alkaptonuria in three of eight couples. All three couples have desired to have children and asked medical help in the past. Hereby, presentation of close relation between alkaptonuria and infertility was pointed out.

Key words: *Alkaptonuria, infertility, ochronosis*

İnfertilite ve Alkaptonüri Arasında Muhtemel İlişki

Alkaptonüri şu ana kadar infertilite ile ilişkisi tespit edilemeyen nadir bir metabolik hastalıktır. Bildirilen bulgular arasında idrar renginde koyulaşma, ciltte okronotik renk değişikliği ve çeşitli kas iskelet sistemi belirtileri vardır. Bu olgu sunumunda birçok üyesinde alkaptonüri ve infertilite problemi olan bir aileyi sunmayı amaçladık. Bu aileden ilk karşılaştığımız hastanın alkaptonüri tanısından sonra infertilite şikayetinin de olduğu anlaşıldı. Histerosalpingografi ve sperm analizi dahil olmak üzere infertilite testleri yapıldı. Detaylı incelemelerden sonra sekiz aileden üçünde alkaptonüri ve infertilite birlikteliği saptandı. Bu üç ailenin de çocuk isteminin olduğu ve daha önce çeşitli tedaviler aldığı tespit edildi. Sonuç olarak da alkaptonüri ile infertilite birlikteliğine dikkat çekildi.

Anahtar kelimeler: *Alkaptonüri, infertilite, okronozis*

INTRODUCTION

Alkaptonuria is a metabolic disease caused by mutations in the homogentisic acid oxidize (HGO) gene causing deficiency in its level, accumulation of tyrosine degradation product-homogentisic acid (HGA), ochronosis, and destructions in the connective tissue. Incidence is estimated to be 1 case in 250,000 to 1 million live births. This inborn error of metabolism has autosomal recessive inheritance (1-4). We reported a family which of several members having alkaptonuria and infertility.

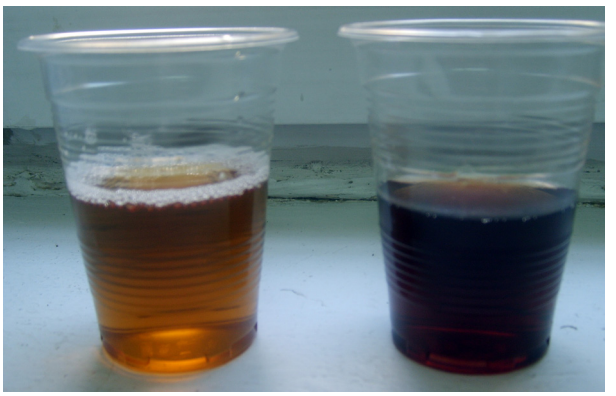

***Figure 1**. Darkened urine after 5 to 10 minutes waiting*

CASE

Main symptom for admission of the first patient we deal with was back pain and darkening of the urine upon waiting (Figure 1). Second and third degree relatives of this patient were also suffering from similar problems. They had thoracic kyphosis, loss of lumbar lordosis and limitation of back movement. Plain films of lumbar and thoracal spine showed narrowing of the intervertebral spaces, multiple disc calcification and vertebral body osteoporosis. Laboratory revealed blood and urine sample results consistent with the diagnosis of alkaptonuria (Table 1). Generalized degenerative changes associated with osteophytes were present. Degenerative changes of the spine were far more advanced than would be anticipated for the patients' age. Using analgesic and antiinflammatory drugs and rehabilitation program including physical therapy and exercise were diminished their complaints. Infertility was the accompanying symptom of the first patient beside these musculoskeletal complaints. Totally we investigated eight families including sixteen persons and all had diagnosis of alkaptonuria. Among them, three families had infertility problem. These couples have undergone detailed infertility investigations including hormone profile and hysterosalpingography in the past.

Along the treatment of infertile couples, clomiphene citrate and recombinant FSH treatments have been useless. Other medical histories were unremarkable. Another interesting issue for this family was consanguineous marriage.

DISCUSSION

All members of the family were second or third degree relatives. Since alkaptonuria is an autosomal recessive disease, consanguineous marriage may be the reason of high incidence in this family. Although we hypothesized relation of the alkaptonuria with infertily, also determined that; neither all infertile couples have alkaptonuria nor all alkaptonuria couples are infertile. The region where this family lives is a part of country having high fertility rate (above 4). For this reason and also according to the investigations it is feasible to say that all couples in this family desire to have children. Also we know that these infertile couples have not used any contraceptive method.

***Table 1**. Urine and serum analysis of the patients with infertility.*

Couples	*Urine*		*Serum*	
	Alcaptonurine µg/ml (0-4 µg/ml)	*Homogentisate g/day (0-2.5 g/day)*	*Homogentisate g/day (2.4-12 ng/ml)*	*Tyrosine µM (5-250 µM)*
Male 1	*16.3*	*4.6*	*18.7*	*530*
Female 1	*12.9*	*3.9*	*17.2*	*375*
*Male 2**	*14.2*	*3.8*	*15.5*	*425*
*Female 3**	*15.0*	*4.1*	*19.1*	*550*

** Wife of couple 2 and man of couple 3 deceased.*

HGO deficiency causes large amount of HGA excretion through urine turning into dark over time (1), which is the major symptom for diagnosis of alkaptonuria. This darkening is the result of oxidation and polymerization of the HGA in an alkaline medium. As a matter of fact, acid urine may not darken unless it is kept waiting. Hence darkening of the urine can not be noted in several under-diagnosed patients. The main clinical symptom is degeneration of the articular cartilage. Osteoarthritis, scoliosis and fusion of the vertebra can be observed in further stages. Pigment deposition can cause valvular abnormalities of the heart. There is no definitive therapy for this disease, however protein restriction- especially phenylalanine and tyrosine- and ascorbic acid treatment are advised to diminish plasma HGA levels.

In the previous literature, findings are related with HGA deposition especially in musculoskeletal and cardiovascular system in addition to urinary darkening due to homogentisic aciduria. Furthermore prostatic calculi (2) and urinary lithiasis (3) and vaginal hyperpigmentation (4) are among other reported manifestations. Up to now preferential site for pigment deposition has been indefinite. Infertility affects approximately 15% of couples (5). The etiologies of infertility in couples include ovulatory dysfunction (15%), tubal and pelvic pathologies (35%), male factor (35%), unexplained infertility (10%) and other factors (5%) (6). Therefore still approximately 15% of the couples remain to be diagnosed.

In the pertinent articles we could not come across any information related with association of alkaptonuria and infertility. We likeminded that alkaptonuria may become one of the problems causing infertility. There are many idiopathic infertility patients and an expected high percentage of undiagnosed alkaptonuria patients exist. These two groups of patients may have been intercepted in a certain rate.

REFERENCES

1. *O'Brien W, La Du B, Bunim J. Biochemical, pathologic and clinical aspects of alcaptonuria, ochronosis and ochronotic arthropathy: review of world literature (1584-1962). 34 ed. 1963. p. 813-38.*
2. *Concepcion MT, Banares BF, Traba ML, Rodriguez de Minon Cifuentes JL. (Alkaptonuria, prostatic calculi, and ectopic ureter). Actas Urol Esp 1997 Feb;21(2):167-70.*
3. *Van Offel JF, De Clerck LS, Francx LM, Stevens WJ. The clinical manifestations of ochronosis: a review. Acta Clin Belg 1995;50(6):358-62.*
4. *Gatcliffe TA, Soto-Wright V, Kasznica J. Vaginal hyperpigmentation due to ochronosis. Obstet Gynecol 2003;101(5 Pt 2):1066-8.*
5. *Mosher WD, Pratt WF. Fecundity and infertility in the United States: incidence and trends. Fertil Steril 1991;56(2):192-3.*
6. *Female infertility. In: Speroff L, Glass R, Kase N, editors. Clinical gynecologic endocrinology and infertility. 6 edn. Baltimore, Maryland: Lipincott Williams & Wilkins; 1999. p. 1020-1.*