HİDRANSEFALİ: CLOMIPHENE ILE YAPILAN OVULASYON İNDÜKSIYONUNUN SONUCU MUDUR?

İki Olgunun Bildirisi

HYDRANCEPHALY : Is a result of clomiphene induced ovulation ?
Two Cases Report

Hakan Hadi KADIOĞLU, Mehmet Dumlu AYDIN, Berrin G. KADIOĞLU
İsmail Hakkı AYDIN

Atatürk University Medical School, Department of Neurosurgery (HHK, MDA, ŞHA) and Department of Obstetric and Gynecology (BGK), Erzurum-Turkey

Özet

Hidransefali, serebral hemisferlerin tahrip olup içinde beyinomurilik sıvısı içeren ve kabaca poliporensefali olarak düşünülebilecek membranöz bir kesenin oluştuğu nadir bir intrauterin ansefalopatidir. Günümüzde anovulatuar kadınlarda fertiliteyi düzeltmek amacıyla yapılan ovulasyon indüksiyonunda clomiphene citrate yaygın olarak kullanılmaktadır. Bu amaçla clomiphene alan bazı annelerin bebeklerinde bir kısım merkezi sinir sistemi anomalileri bildirilmiı olmasına karşılık hidransefali bildirilmemiştir. Bu bildiride, anneleri hamilelik öncesi ovulasyon indüksiyonu için clomiphene alan ve baş çevrelerinde büyümenin olmasından ötürü pediatrisyenlerce polikliniğimize gönderilen 2 olguyu sunarak, literatür derlemesi ile tartıştık.

Anahtar kelimeler: *Clomiphene, Doğmalık anomali, Hidransefali, Ovulasyon indüksiyonu*

Summary

Hydrancephaly is a rare intra uterin encephalopathy, in which the cerebral hemispheres are destroyed and transformed into membranous sac containing cerebrospinal fluid and may be thought as a gross polyporencephaly. Today clomiphene citrate is used extensively to induce ovulation in an anovulatory female to improve fertility. Some central nervous system abnormalities in patients whose mothers had received clomiphene as an ovulatory stimulus were reported, but hydrancephaly has not been. In this paper, we presented two infant with enlarged head circumference who were referred to the outpatient department of neurosurgery by pediatricians. The mothers of infants had used clomiphene, pregnant ovulation inductors, before pregnancy. These 2 cases are presented and discussed with reviewing of literature.

Key words: *Clomiphene, Congenital anomaly, Hydranencephaly, Ovulation induction*

AÜTD 1995, 27:100-103 **MJAU** 1995, 27:100-103

Introduction

Virtuel absence of the cerebral hemispheres except for basal part of occipital and sometimes the temporal poles is defined as hydrancephaly, the most severe form of porencephaly impliying a destructive and encephaloclastic process (1,2). The residual brain usually consists of a normal brainstem, cerebellum, small but distinct basal ganglia and remnant of cerebral cortex, compressed and collapsed against the floor of the supratentorial compartment. The occipital lobes, in particular, are usually visible on computerized tomography (CT) (3,4).

Neural tube defects can occur after ovulation stimulation with clomiphene citrate (CC). However, an association between drug and these defects has not been established. Congenital malformations reported in patient who received CC prior to conception include; hydatyform mole, syndactyly, pigmentation defects, congenital heart defects, Down's syndrome, hypospadias, hemangioma, retinoplasia, clubfeet, microcephaly, clip palate, polydactyly, anencephaly (5-24). Hydranencephaly has never been reported with receiving CC prior to conception.

It is well established that CC is capable of inducing ovulation in anovulatory women. However, there are some reports on possible teratogenicity of CC. The reported incidence of malformations following CC-induced ovulation is quite variable (25).

In this paper, we describe two infants with developmental delay, congenital cerebral anomalies and enlarged head circumference, two infant's mothers had used CC as an ovulatory inductors.

Case Reports

Case 1: The patient is 4-year-old male and second-born child of the parents in their late twenties. Their first child died from an unknown cause when she was 3 months old. The parents were far-relative and the mother had used some different ovulation inductor drugs to be pregnant for 7 years and she had viral upper respiratory tract infection at second trimester of her pregnancy but no medication was taken. The pregnancy was otherwise uneventful. A male infant

Figure 1. *CT scan of Case 1*

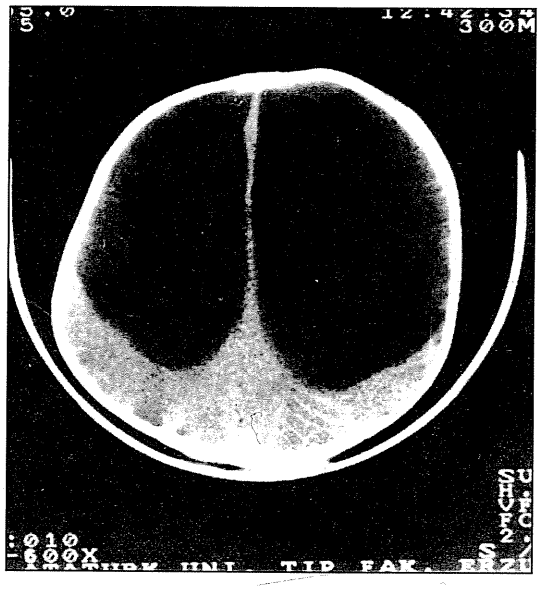
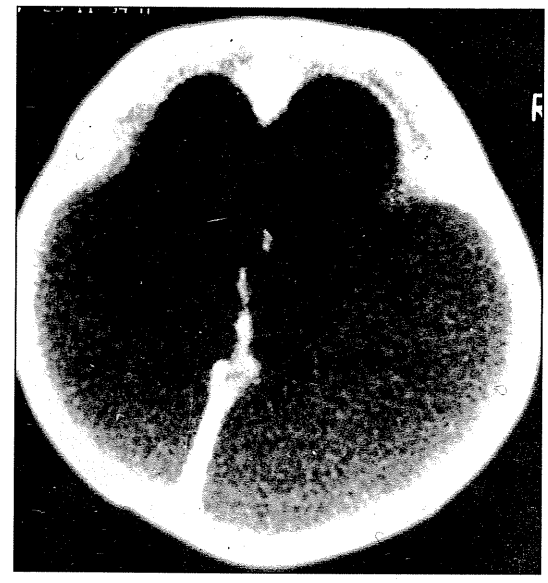


Figure 2. *CT scan of Case 2*



was born spontaneously, but with some difficulty at home. The duration of gestation Apgar scores, bithweight, lenght and head cicumference was not exactly known. His parents first noticed a developmental delay at the ten months but they did not prompted to seek medical advise. They firstly noticed the enlarged head at the two years old but did not need to seek medical advise. Before admission to our Department, the child had been hospitalized at the Pediatric Clinic of State Hospital of Erzurum for a while because of covulsive attacksand subfebril fever, after then referred to the Neurosurgery Department of Research Hospital of Medical School of Atatürk University.

On admission at 4 years old, head circumference was 56 cm., weight 13 kg. The physical examination revealed total paralysis, setting sun sign at the eyes and enlargement of head cicumference. The blood and urine analysis normal. CT scans of the brain showed hydrancephaly (Fig.1).

Case 2: This was 3.5 month old female infant and she was the first born child of nonconsanguenous healthy young parents. The mother had used only clomiphene to be pregnant, which was prescribed by an obstetricians. Family history is otherwise unremarkable.

The parents first noticed the enlargement of head and admitted to the State Hospital and to the several private pediaticians and took medical advises and therapy for convulsive attacks. While she was 3.5 months old, she was referred to the outpatient clinic of our department by a pediatrician. On admission, head circuference was 59.5 cm. and the eyes were rotated to downward position, producing setting sun sign, newborn reflexes were inactive. On CT scans the hydrancephaly was shown (Fig.2).

Discussion

Hydrancephaly is a devastating central nervous system malformation. It is not vell defined, very rare disorder (0.5 per thousand births).The exact etiopathogenesis is not known. It can be classified as a circulatory encephalopathy. Two opposing theories are generally advanced the encephaloclastic or destructive theory and the theory of dysontogenesis or malformation, due to early disruption of organogenesis. It has many causes (vascular, viral, parasitic, genetic, toxic, estrogenic, etc.). It can be caused by intra-uterin occlusion or disease such as toxoplazmosis and citomegalovirus disease, in which part of cerebral each hemispheres are destroyed (1,2,4,26-30).

The formation of cavites as the result of a hypoxic-ischeamic injury is peculiar a response to the developing fetal brain, in which the macrophage reponse to cell death is present but the neuroglial response is still developing. In this respect hydrancephaly may be considered the most severe form of destructive encephalopathy, leading to the disappearance of nearly all structures, including the ventricular walls, leaving only a small zone of residual glial tissue underneath the pinela, the pia-arachnoid (13).

Destruction of cerebral mantle in the embrional period may lead to huge porencephalic defects (*encephaloclastic porencephaly*), with subsequent failure of development of brain in the marginal parts of porencephaly, the cortex is malformed, but this indicates only that the lesion preceded neuronal migration. Lack of resistance of the defective brain to ventricular pressures enlarges the head. Still in other cases, there appear primary failure of development, more specificially, varying degrees of evagination (1).

It is usually believed to be due to a vascular accident early in utero with complete or nearly complete infarction of the territories of the brain supplied by middle cerebral and anterior cerebral arteries. The exact causative factor or factors are not known (3,4,30).

It is well known that many central nervous system abnormalities with or without other system congenital malformations occur after ovulation stimulation and estrogen intake in early gestation time (5-18,20-23).

Traditionally, teratogenic effects of drugs have been noted as anatomic malformations. It is clear that these are dose and time related and the fetus great risk during the first 3 months of gestation. However, it is possible for drugs and chemicals to exert their effects upon the fetus at other time during the pregnancy. The mechanisms of teratogenic agents are poorly understood, particularly in human. Drugs may affect maternal tissues with indirect effects upon the fetus may have direct effect on the embryonic cells and the result in specific abnormalities. Drugs may affect the nutrition of the fetus by interfering with the passage of nutriments across the placenta. Alterations in placental metabolism influence the development of the fetus since placental integrity is a determinant of fetal growth.

It is established that CC is capable of inducing ovulation in anovulatory women. However, several case reports have linked CC with congenital malformations, especially neural tube defects (NTDs) and anencephaly (6,7,10,12,18,22). But hydrancephaly has never been reported after induced ovulation by CC.

The incidence of children born with congenital malformations (major and minor) is 32.5 per 1000 births (5,14-16,25). Two hypotheses were suggested: a-) It is speculated that NTD may be a result of a fetus-to-fetus interaction between two dizygous twins who do not share certain gene-based recognition characters. In the presence of certain environmental factors, such twins might interact so that one would be eliminated and the other sustain a NTD (32). In contrary that, Shoham et al claim that this hypothesis does not seem acceptable because, although the dizygotic twinning rate in normal population rises both with maternal age and parity, no such relationship is seen with NTDs (33). b-) Field and Kerr presumed that underlying anovulation possibly associated with aging of the ovum is common to twinning, subfertility, and CC therapy (12). Dyson and Kohler reported anencephaly after ovulation stimulation by CC (10). They noted the possibly that the malformation was associated with subfertility (which the drug alleviates) rather than with the drug itself. Sandler also presumed that an aged ovum or an aged sperm may have been involved in this pathology (22). In addition, James said that the couples who produce anencephlics may be subfertile; one would therefore expect anencephalic births to be associated -but not causally- with the administration of all drugs designed to alleviate subfertility (18). And Barret and Hakim suggest that the possibility of a causal relationship between ovulation-stimulating treatment and central nervous system abnormalities exist (6). Elwood also think that the CC acts via a mechanism which increases the risk of anencephaly and dizygotic twinning is due to double ovulation (11).

In contrary that, some authors refuted the concept which congenital central nervous system abnormalities result in following CC-induced ovulation. They proposed that CC has no teratogenic effect and the babies born after CC-induced ovulation are not no increased risk malformations as compared with normal population (14-16,21,25,33-39).

The first infant's mother used many different drugs for long time. But she had used clomiphene and another drug which we were unable to learn its name or consistency prior to conception. The second infant's mother noted that she had used only one ovulation inductor, clomiphene, before pregnancy, but she stopped to take when she recognised her pregnancy. The hydrancephaly of this infant can be related to this ovulation inductor agent, clomiphene. Clomiphene is contraindicated after conception has occured. But the mother of infant said that she did not used more after recognised her pregnancy. It is interesting that both of infants have not had another congenital anomalies, whereas congenital anomalies are usually multiple. In advertent use of clomiphene in the first trimester has been reported in two patient. A ruptured lumbosacral meningomyelocele was observed in one infant exposed during the 4th week of gestation. There was no evidence of hydrancephaly, even hydrocephalus. The second infant was delivered with oesephageal atresia with fistula, congenital heart defects, hipospadias, absent left kidney. The mother also took methyldopa throught pregnancy for mild hypertension (9).

First infant's parents were far-relative and the mother has had viral upper respiratory tract infection and her first child had dead while she was 3 month old with unknown cause. These can be etiologic factor or factors. It has never been reported the hydrancephaly after using clomiphene with pregnancy or prior to conception. If the cases with hydranencephaly we reported are really related to that nonhormonal fertility agent clomiphene, these are first cases after using that agent in the literature. To be sure with that result, it is required more and detailed experimental studies.

We believe that the incidence of hydranencephaly after using clomiphene prior to conception or after conception has occured, whatever the reason may be, the mother of infant with hydranencephaly should be asked whether she had used clomiphene or any ovulation inductor prior to conception or after conception has occured. Patient requiring the use of clomiphene should be cautioned that each new course of drug should be started only pregnancy has been

excluded, because it is contraindicated after pregnancy has occured.

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Correspondence Adress:

Hakan Hadi Kadıoğlu , MD
Atatürk University Medical School, Neurosurgical Department, 25240-Erzurum,TURKEY