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Unforeseen risks on the quest to fertility: A case report of a cerebral venous sinus thrombosis in a man on fertility treatment with clomiphene citrate

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Introduction

Clomiphene citrate is a selective estrogen receptor modulator that is widely used in the treatment of infertility in both male and female populations [1]. While its use in the female population has been widely studied and is used in the management of a wide array of medical conditions, especially those associated with ovulation, its use in the male population remains controversial. It has been used as an off-label medication in the management of male infertility and hypogonadism since the 1970s but its efficacy has not been well established [2]. Its side effect profile and complications are poorly studied and reported in modern literature. Here we present a case of a man who developed a superior sagittal sinus thrombosis while on antifertility treatment while on fertility treatment with Clomiphene citrate. Intracranial venous thrombosis is a rarely documented side effect of clomiphene citrate and has been previously documented in only 2 case reports [3,4]. This prompted us to report this to the medical world to help increase the literature on this rare but devastating side effect of Clomiphene treatment.

Case presentation

A 40-year-old gentleman presented to our Emergency Department with a 4-day history of headaches which was followed by right sided upper limb weakness. On the day of admission to our hospital he had multiple episodes of generalized tonic-clonic seizures. The patient had a history of infertility. He had been diagnosed with oligozoospermia and had been started on treatment with Human Chorionic Gonadotrophin Injections at 2000 IU every 10 days. He had received 4 doses of the same. His urologist had also started him on Clomiphene Citrate tablets (at a dose of 25 mg once daily) which he has been taking since the last 30 days. The patient did not have any other co-morbidities. He was not a known smoker or alcohol consumer. Family history was significant for a Myocardial Infarction in his father at the age of 60. Initial examination revealed some paucity of his right upper limb but it was otherwise normal. APTT and PT/INR at admission were normal. Fundoscopic examination revealed grade 2 papilledema changes. The rest of the systemic examination was normal.

Investigations

MRI done before arrival had shown a Superior Sagittal sinus thrombosis. MRI Brain with Magnetic Resonance venogram was done in our hospital and revealed thrombosis of the superior sagittal sinus and a few adjacent cortical veins. It also showed long TR Hyperintensities in the cortex and subcortical white matter of the right frontal region, Cytotoxic edema in the cortex and subcortical white matter of the right high frontal region, left pre and post-central gyrus and left parietal region with venous congestion in the bilateral frontal and parietal regions. The bilateral optic nerves also appeared tortuous with peri-optic flaring with flattening of the sclera posteriorly with a partially empty sella which was suggestive of raised intracranial pressure changes.

The routine blood investigations were normal. Thrombophilia work up and genetic markers for thrombosis was done which showed elevated levels of factor VIII, mild positive lupus anticoagulant and heterozygous mutations in MTHFR C677T and KNG1 T1742C genes and homozygous mutations in SerpinC1 G786A gene.

Differential diagnosis

Since our patient had presented with severe headache and seizures, we considered differential diagnoses of cerebral venous thrombosis, subarachnoid hemorrhage, tumor with mass effect, and AV Malformations. MRI brain helped rule out structural causes for the headache and the MR venogram helped confirm the diagnosis of Cerebral venous thrombosis.

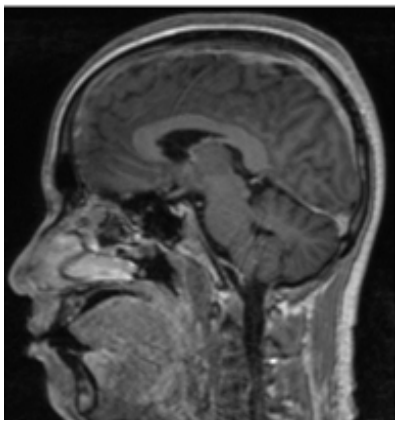

Figure 1: MR Venogram showing thrombosis of the superior sagittal sinus.

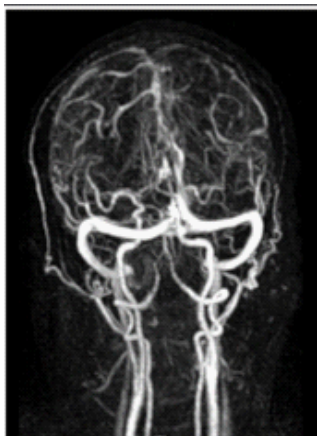

Figure 2: Three-dimensional reconstruction MR venogram showing thrombosis of the superior sagittal sinus and a few adjacent cortical vein.

Treatment

Patient was treated with anti-edema measures, and anti-epileptics. Systemic anti-coagulation with enoxaparin (60 mg subcutaneously twice daily) was given for the first 5 days and then oral anticoagulation with warfarin with dose adjusted INR was continued. The diagnosis was explained to him and he was advised to stop taking Clomiphene and Human chorionic gonadotrophin. His sensorium improved, he did not have further seizures, and his right upper limb power improved during his stay in the hospital and was discharged in stable condition. On follow up the repeat lupus anticoagulant was negative. We are planning to continue the dose adjusted warfarin for a period of 6 months to one year, Repeat the factor VIII levels while off anticoagulation and if this is normal to discontinue the oral anticoagulation.

Discussion

Cerebral Sinus Venous Thrombosis is a potentially fatal neurological condition that is often underdiagnosed due to its nonspecific presentation. Although the autopsy series approximates the incidence to be 3-4 million cases per million, clinical series have shown a 10-fold increase in these numbers. The estimated female-to-male ratio was 3:1 and comprises 0.5-0.1% of all stroke occurrences. An increased incidence is seen among children, younger adults, females of the reproductive age group, and low-income countries [5].

The most common form of CSVT is the subacute type, which constitutes almost half of all the cases, and the chronic form is less frequent. The ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis) determined the occurrence of CSVT in various sites - transverse sinus (86%), superior sagittal sinus (62%), straight sinus (18%), cortical veins (17%), jugular veins (12%), vein of Galen, and internal cerebral vein (11%) [6].

We report a case of a young man with no other risk factors other than antifertility treatment with clomiphene citrate and HCG injections.

Our patient had been taking Clomiphene for the treatment of oligozoospermia. Clomiphene citrate is a selective estrogen receptor modulator. Clomiphene citrate has been used as a treatment for subfertility in women. Although showing mixed results when it is used to treat infertility in men [7,8], it has shown benefits in men with hypogonadism [2] as low doses of clomiphene have resulted in improvement of the testosterone/oestradiol ratio [9]. It also stimulates endogenous androgen production. Thus, it can be used as an alternative to testosterone for male hypogonadism. Its use in men is not approved by the FDA but is prescribed off-label with Human Chorionic Gonadotropin (HCG) to elevate total testosterone levels and to maintain spermatogenesis in hypogonadal men.

Common side effects of Clomiphene include headaches, hot flashes, nausea, dizziness, visual disturbances, weight gain, and fluid retention. Clomiphene is also well known to cause gastrointestinal symptoms and endocrine disorders. It is associated with venous thrombosis, DVT, and central retinal vein thrombosis in women with various risk factors and rarely causes ovarian hyperstimulation [10-12].

An extensive literature review revealed only two other case reports documenting an intracranial venous thrombosis in

young men taking Clomiphene citrate for infertility issues.

The first case report documented a patient in his mid-30s who presented with a history of headaches and was subsequently found to have a sub-acute clot in the torcula extending to the left transverse sinus and into the left sigmoid sinus extending into the posterior aspect of the superior sagittal sinus. He had been taking clomiphene (at a dose of 50 mg per day) for 3 weeks, which was a similar time frame to our case patient [3].

The second case report found during review documented a 31-year-old who presented with a generalized tonic-clonic seizure, who had been taking low dose Clomiphene citrate (at 25 mg/day, a similar dose to our patient) for 3 months. Imaging for this patient had shown lesions involving the left high cortical sulci and prominent superficial cortical veins and an absence of vein of Troland [4].

The literature review also revealed case reports of male patients undergoing clomiphene treatment presenting with thrombosis in other sites like a report of Central retinal vein occlusion in a male carrier of factor V Leiden [13] and pulmonary embolism [14].

Since the patient was also on injectable Human chorionic gonadotrophin, we considered it as a risk factor too. However, despite extensive literature review, we were unable to find any cases of patients with no other risk factors developing thrombosis on injectable HCG. While there was a reported case of cerebral venous sinus thrombosis in one patient using HCG for super-ovulation [15], and one case with multiple Deep vein thrombosis in a patient using HCG for weight loss [16], these incidents occurred in female patients and the mechanism of action for the thrombi formation was proposed to be due to hyperovulation. All this led us to consider Clomiphene citrate as the main agent for the thrombi formation in our patient.

Conclusion

Despite it's use as a fertility agent since the 70s, the side effect profile of clomiphene citrate is still poorly understood in males. More research is needed to determine if the risk of thrombosis is elevated in males taking clomiphene. Cerebral venous thrombosis, though rare, should be considered as a side effect of clomiphene in a patient presenting with headache and blurred vision.

More research also needs to be done into whether there is a synergistic effect between Clomiphene citrate and HCG which may increase risk of thrombi formation, especially in the background of genetic mutations associated with decreased anticoagulation activity.

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