

Tibial Agenesis and Gollop-Wolfgang Complex in Three Siblings Born to an Epileptic Woman Treated with Carbamazepine: Teratogenicity?

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Abstract

The term "limb deficiency" incorporates absence and/or size reduction of any of the 120 human limb bones, with around 205 identified nosologic entities. Of these, the Gollop- Wolfgang Complex (GWC) is a rare abnormality comprising absence of tibia and ipsilateral forked femur with ectrodactyly. There is scarcity of literature implicating antiepileptic drugs in the etiology of GWC but the teratogenicity of antiepileptics especially valproate is well documented. The management of epilepsy during pregnancy requires a balance between control, the risks involved in uncontrolled seizures and the teratogenicity of antiepileptic drugs. This study presents three siblings with GWC and tibial agenesis whose epileptic mother had been on treatment with carbamazepine for 10 years. To the author's knowledge, this is the first time that carbamazepine has been implicated in causation of GWC/tibial agenesis.

Introduction

Gollop-Wolfgang Complex (GWC) is a rare congenital limb anomaly characterized by tibial aplasia, ipsilateral bifurcation of the thighbone and an ectrodactyly [1]. It is often associated with other anomalies of limbs, heart, digestive and urinary tracts and the lumbosacral vertebrae [2,3]. Congenital absence of tibia is a rare and severe lower limb malformation with an incidence of approximately 1:1,000,000 live births [4,5]. Anomalies like Tibial hemimelia with split hand/foot malformation (TH-SHFM) and Gollop-Wolfgang complex are rarer malformations with highly variable manifestations. The first case with this pattern of malformations may have been reported by Sir Ambrose Pare in 1575 [6]. GWC is a form of tibial field defect, which includes distal femoral bifurcation, tibial agenesis, oligo-ectrodactylous toe defects or preaxial polydactyly, occasionally associated with hand ectrodactyly. The etiology of GWC is still unclear [7]. This study presents three siblings suffering with GWC whose mother had been treated with carbamazepine for more than decade for grand mal epilepsy. There was no history of any skeletal deformity in both parents' families prior to these three sibs.

Clinical Report

Patient 1

The first born child (a girl) of a 32 year old mother without malformations, with normal karyotype (46 XX) had GWC. There was no documented consanguinity with the father, no similar family history, no history of radiation exposure; the mother was a grand mal epileptic and had been taking carbamazepine without folate supplementation prior to and during pregnancy. The child had bifurcated left distal femur with right tibial agenesis, plus right knee subluxation, clubfoot and hypoplasia of the first ray of the right foot (Figure 1). She could sit without help but it was impossible for her to stand upright without support because of functional disability of the right lower limb. At the medial distal third of the left femur, a large bony protuberance was present having a width of 13 cm and a length of 5 cm. The patella was not palpable. The right leg was thinner and shorter than the left. There was no visible medial malleolus. The right foot was in varus equinus position. Radiograph of the left lower limb (Figure 2) showed a bifurcation of the distal 1/3 of the femur and on the right, agenesis of the patella, tibia, astragalus and first metatarsal.

Patient 2

This boy was the middle sib, a male who presented with bilateral ectrodactyly of hands and feet, bilateral tibiofemoral agenesis and inability to move around unless he dragged himself (Figure 3).

Patient 3

The youngest child, a girl with with bilateral ectrodactyly of hands and feet, bilateral tibiofemoral agenesis and congenital pseudoarthrosis of the left tibia (Figure 4, 5 and 6).

Economic constraints precluded the gene mapping and



Figure 1: Photograph of patient 1, a female (the first and eldest).

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Received September 04, 2013; Accepted September 05, 2013; Published September 10, 2013

Citation: Muzaffar N (2013) Tibial Agenesis and Gollop-Wolfgang Complex in Three Siblings Born to an Epileptic Woman Treated with Carbamazepine: Teratogenicity? Genetics 2: 118. doi:10.4172/2161-1041.1000118

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Figure 2: Radiograph of patient 1 showing right tibial aplasia and left femoral duplication.



Figure 3: Photograph of patient 2, a male with bilateral ectrodactyly of hands and feet and bilateral tibiofemoral agenesis.

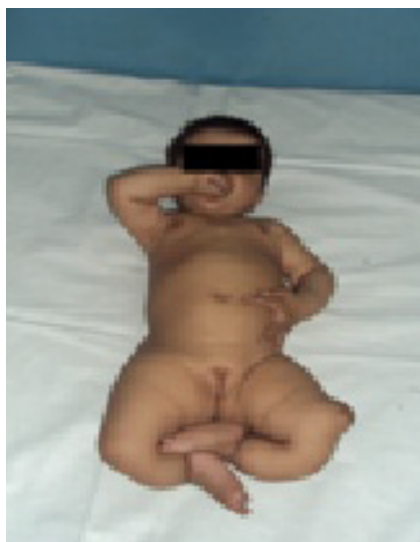


Figure 4: Photograph of patient 3, a girl with bilateral ectrodactyly of hands and feet, bilateral tibiofemoral agenesis and congenital pseudoarthrosis of the left tibia.



Figure 5: Radiograph of patient 3.



Figure 6: Photograph of all three siblings (L-R patient 3,1,2).

Discussion

Children who have been exposed to antiepileptics (AE) in the womb are at higher risk of congenital malformations including limb defects [6]. To avoid these risks, the common strategy has been to use the AE as monotherapy and in the lowest possible doses during pregnancy. Tibial agenesis-ectrodactyly or GWC syndrome is one of the most severe limb defects. Inheritance appears to be autosomal dominant with reduced penetrance [8]. In 1980, Gollop described two brothers with ectrodactyly in one hand, unilateral femoral bifurcation, absence of both tibia and foot monodactylia. In 1984, Wolfgang reported a tibial hemimelia with ipsilateral femoral bifurcation and contralateral tibial diastasis [9]. In 1986 he introduced the eponym of Gollop-Wolfgang complex and concluded that the association is not incidental [10]. According to literature data, no specific etiology has been found for this malformation. The almost constant absence of the tibia led Kotakemori and Ito [3] to suggest that it could be a result of an ectopic implantation of the tibia in the femur. However the observation of Ostrum et al. [11] of a child with GWC and a normal tibia excludes this hypothesis. Balog and Skinner [12] in 1984, reported a case of a left femoral duplication, where there was hydroxysine ingestion during the first four weeks of gestation. Proper management of a pregnant woman with epilepsy requires knowledge of the risks and effects on the same seizures and the effects that may occur by taking antiepileptics (AE). The management of epilepsy during pregnancy requires a balance between control of the mother and the risks involved in uncontrolled seizures, versus the teratogenicity of antiepileptic drugs [13]. Furthermore, folate supplementation has been shown to reduce congenital defects [14]. Sodium valproate has been implicated in most of these cases of congenital malformations [13-15] but till date, carbamazepine has not been directly implicated in GWC.

Jones et al. [16] classified tibial hemimelia based on initial radiographs. Four types of deformity were recognized. In type I,

chromosomal study of the family and serological study of carbamazepine in the mother and her children. We could not assess the family for surgical intervention as the same was too costly for the parents. They did not want to go for amputation either. They have been counseled to avoid further pregnancies.

the tibia is not visible. In type 1a, the tibia is completely absent with a hypoplastic distal femoral end. In type 1b, a rudimentary tibia articulates with a relatively normal distal femoral end. In type II, the proximal tibia is preserved with a short tibial segment, but the distal tibial end is absent. In type III, the proximal tibia is absent. In type IV, a short tibia with distal tibiofibular diastasis is present. In patients with a congenital absence of the tibia, accurate diagnosis is of the utmost importance in planning future treatment. In the absence of proximal tibial anlage, especially in patients with femoral bifurcation, the knee should be disarticulated. Tibiofibular synostosis is a good choice in the presence of a proximal tibial anlage and good quadriceps function. The treatment of femoral bifurcation is simple—to resect at its base. However, the treatment of tibial hemimelia is challenging. Amputation, fibular transfer, or reconstruction procedures are the alternative treatment options [10].

The association of GWC and antiepileptics has been well documented [15,17] especially where the mother was on valproate therapy. As such, there is no documented case of carbamazepine therapy causing GWC. However, Guven et al. [15] reported a child exposed prenatally to valproate and carbamazepine presenting with severe bilateral upper limb defect and phenotypic features of fetal valproate syndrome. Carbamazepine has been known to cause neural tube defects like spina bifida and it is not improbable that in our series, the increasing severity of the disorder with successive siblings brings us to the hypothesis that prolonged therapy with carbamazepine may progressively increase expression of some abnormal gene load which manifests with increasing severity in successive childbirths. The unusual combination of fetal carbamazepine exposure and GWC could have been passed off as coincidental in our patients. However, the presence of similar field defects in sibs in the absence of any other known trigger raise the possibility of molecular events triggered by carbamazepine toxicity leading to a phenocopy of tibial agensis, with GWC can be speculated. We think that a partially penetrant autosomal dominant gene interacting with carbamazepine may have caused the bony defects since those have not been part of the spectrum of human birth defects post-carbamazepine.

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