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CASE REPORT

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Wieacker-Wolff syndrome, a distinctive phenotype of arthrogryposis multiplex congenita caused by a "de novo" *ZC4H2* gene partial deletion

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Abstract

Unusual fetal arthrogryposis on ultrasound should draw attention to look for additional lower limb anomalies. Precise genetic counseling may be obtained from deletion on Xq11.2 as for *ZC4H2* gene sequencing diagnostic for Wieacker-Wolff syndrome.

KEYWORDS

arthrogryposis multiplex congenita, Wieacker-Wolff syndrome, Xq11.2 deletion, *ZC4H2* gene

1 | INTRODUCTION

Arthrogryposis multiplex congenita (AMC) defines a phenotype of limited limb mobility when contractures are present in ≥2 joints with muscle contractures. Incidence is 1 in 3000–5000 living births.[1] Monogenic conditions/cytogenetic CNV are involved in a wide range of AMC[2] responsible for hypo/akinesia: mutations in over 800 genes are identified among which 150 are X-linked.[1] A distinct X-linked syndromic form was originally described by Peter Wieacker and Gerhard Wolff in males with "club feet": 6 related males presented AMC with variable degrees of intellectual disability, motor retardation, ophthalmic dyspraxia, and progressive muscle atrophy[3] (OMIM #314580). Intragenic deletions/point mutations in *ZC4H2* gene have been confirmed in the original family as in other patients.[4,5] Syndromic presentation associated with the presence of *ZC4H2* gene variants are known as "ZARD" ("ZC4H2-associated rare disorders"). From 48 males and 57 females inside 42 families so far reported, females may be affected as well.[1,6-9] Prevalence is estimated to be <1/1,000,000.[6] Of note, females with "de novo" variants may develop variable degrees of mild-to-severe learning disability. Although precise genotype/phenotype correlation is not obtained, females with "de novo" Xq11.2 microdeletions and haploinsufficiency/loss-of-function of the protein are prone to a more severe phenotype. Speech delay/ absence of speech are almost constant.[1] Additionally, phenotypic features appeared to be constantly present: a high forehead, rotated ears, flat philtrum, metacarpophalangeal contractures, camptodactyly, club feet, and distal limb muscle atrophy, hip dislocation, and/or joint flexion contractures.

To date, prenatal presentation was reported in five unrelated fetuses.[1] The available phenotype—two males and three females—encompasses clubfoot/feet, hypo/

akinesia, rocker-bottom feet, contractures, AMC, and edema. These features were recorded during the third trimester. Complete ultrasound evaluation showed normal growth parameters, absence of any additional anomaly but for one fetus with cryptorchidism and micropenis.

The pregnancy of a healthy woman was referred to our tertiary center when first-line obstetrician diagnosed on ultrasound "unusual" arthrogryposis made of unilateral left clubfoot and reduced right upper limb movements with normal global vitality at the gestational age of 18 weeks. Patient as partner from Caucasian origin is not consanguineous. There was no personal/family history for contracture, neuropathy, muscle, and/or limb defect neither as for intellectual disability. There was no history of drug exposure, infection, trauma, or vascular anomaly recorded earlier during pregnancy.

The complete ultrasound showed normal growth parameters and no other anomaly but for skin and limb evaluation. On the upper limbs, the right arm was thin and always bent to the chest, the presence of a pterygium was suspected and a clinodactyly on the left hand—fifth finger was noted. On lower limbs, on left leg clubfoot and a thin calf were described; a right thin leg permanently stretched out was recorded (Figure 1). With the images of arthrogryposis together with thin legs, unilateral clubfoot and unusual thin arm folded over the chest, an amniocentesis was performed. Since 2014 in Belgium through the consortium on prenatal diagnosis (BEMAPRE), molecular karyotype represents the first diagnostic approach when congenital malformations are recorded.[10] SNP-array (Affymetrix CytoScan® 750K) identified a heterozygous 262 Kb deletion in Xq11.2 in a female that encompasses exon 1 of *ZC4H2* gene. No contiguous gene deletion was noted. SNP-array to parents confirmed a "de novo" occurrence based on the absence

What is already known about this topic?

Wieacker-Wolff syndrome is a very rare, distinctive form of arthrogryposis multiplex congenita (AMC). To date, only five fetuses are described (prenatal setting).

What does this study add?

We here describe the sixth fetus diagnosed with the Wieacker-Wolff syndrome to draw attention on the ultrasound findings. This clinical hypothesis may lead to encompass differential diagnoses, when AMC is detected as to lead to precise diagnosis and genetic counseling.

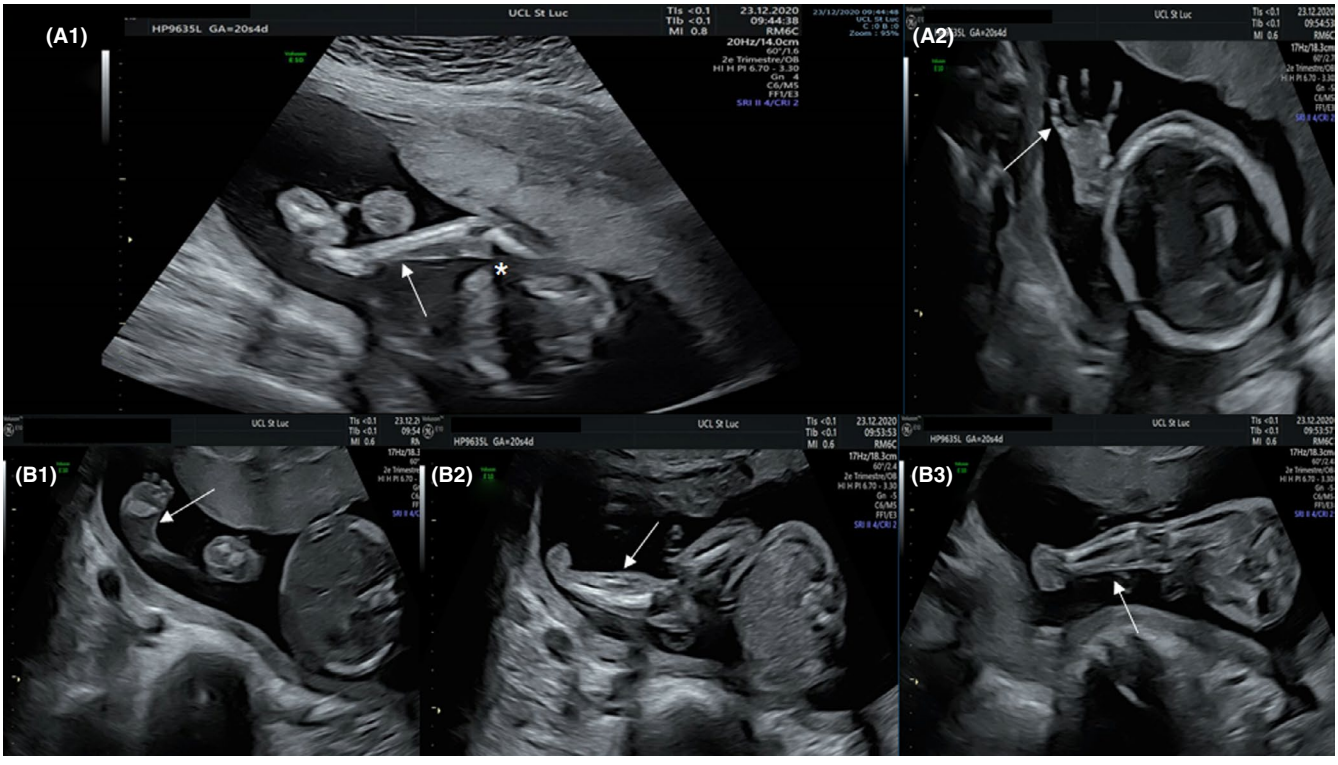

FIGURE 1 20 weeks gestation ultrasound—Voluson E10 General Electric®. (A) Superior limb: (A1) thin right superior limb always bent to the chest; * suspicion of pterygium: (A2): clinodactyly on the left hand—fifth finger (arrow). (B): inferior limb: (B1): left clubfoot (arrow):(B2): thin left calf (arrow): (B3): right thin leg; permanent stretched out (arrow)

of the CNV from parental investigation. Since diagnostic confirmation was obtained for fetal Wieacker-Wolff syndrome and taking into account, an increased risk for possible mild-to-severe intellectual disability parents asked for termination of pregnancy.

Clinical evaluation of this female fetus at gestational age of 26 weeks 3/7 shows a weight of 840 g (P50), a height of 35 cm (P75), and a head circumference of 25 cm (P85). On clinical evaluation were noted a rather short neck, no distinctive facial dysmorphic feature except high forehead and smooth philtrum, normal arm, and forearms on both sides, bilateral camptodactyly of distal phalanges with phalangeal contractures on upper limbs, contractures on both knees, an unusually thin and amyotrophic left leg with homolateral clubfoot and contralateral rocker-bottom foot on lower limbs. Complementary skeletal survey identified hip dislocation only.

2 | CONCLUSION

Present case report underlines the importance of completing the investigation in prenatal diagnosis once AMC is suspected by ultrasound. More precisely, diagnosis of AMC may raise the question on possible unusual form that Wieacker-Wolff syndrome represents. During anatomic second-trimester evaluation, a dedicated screening looking for the presence of camptodactyly or contractures on upper limbs, for amyotrophy/subcutaneous abnormal appearance/asymmetry and clubfoot on lower limb is recommended. *ZC4H2* gene deletion/mutation has to be included in the differential diagnosis of AMC in prenatal setting. Invasive procedure should be completed for molecular karyotype and *ZC4H2* gene sequencing. More precise genetic counseling may then be obtained. Postnatal natural history may be anticipated for the occurrence of intellectual disability, muscle weakness, and ophthalmic dyspraxia; recurrence risk is defined to X-linked germline mosaicism as in present situation, parents do not carry the deletion.

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CONFLICT OF INTEREST
None—mention included in the uploaded file.

AUTHOR CONTRIBUTION
The author and co-authors of the present manuscript have read and validated the present version of the manuscript.

INFORMED CONSENT
Informed consent was obtained and included as upload files—for publication a for images, respectively—an additional ethics approach is not applicable.

DATA AVAILABILITY STATEMENT
Data sharing is here not applicable since no new data have been generated.

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