Reference: Statement

Update: May 2022

Tethered Cord in ZARD

ZC4H2 Associated Rare Disorders (ZARD) [1] (previously referred by as *"Wieacker-Wolff Syndrome"* [2] or *"Miles-Carpenter Syndrome"* [3]*)* is an ultra-rare genetic condition with central and peripheral nervous system involvement caused by deleterious changes (pathogenic variants) of the *ZC4H2* gene. *ZC4H2* is located on the X chromosome and encodes the ZC4H2 (Zinc Finger C4H2-Type Containing) protein essential for normal development. ZARD can manifest in a broad range of clinical severity. Male and female individuals can both be affected.

Understanding of the *ZC4H2* gene functions and the functions of its corresponding ZC4H2 protein is currently limited. It is believed that the ZC4H2 protein plays an important role in the development of the neurologic system during the early stages of human development, particularly through the development of neuromuscular junctions, spinal cord motor-neuron differentiation and neural tube formation. [4,5,6]

Patients with ZARD can have multiple disabilities and health concerns. These can include orthopedic and **musculoskeletal conditions** and **neurological/neuromuscular conditions.** The most common clinical features include: Arthrogryposis Multiplex Congenita, joint defects, muscular atrophy, osteopenia, scoliosis, **tethered cord**, motor planning impairments, mobility impairments, difficulties to eat or breathe, speech disorders, vision problems, epilepsy, global developmental delay. An affected individual can have the full range of symptoms or only a few of them. [1-4,7]

There is currently no cure or effective treatment for this ultra-rare condition. Current treatments consist mainly of different supportive therapies, medical interventions and medications when necessary. [1,7]

To date, there have been 255 diagnosed patients with ZARD worldwide (familiar or de-*novo*).

Although tethered cord in ZARD has not been sufficiently studied till date and there is limited evidence in the current literature [1], we have gathered important knowledge from within our patient community. Anecdotal evidence from our patient community shows that a number of ZARD patients show progressive and debilitating symptoms characteristic of spinal cord tethering. The following symptoms have been reported among our children:
Neurogenic bladder, urine retention, recurrent UTIs, progressive loss of urine and/or fecal control, progressive deterioration of trunk posture, progressive scoliosis, worsening contractures and increasing tone in lower limbs and pelvis, pain, loss of tactile feeling in lower limbs and feet, tiptoeing, instigated and spontaneous clonus of lower limbs and legs.
In almost all cases, the symptoms appear around 4 to 6 years of age and have been reported to appear either suddenly or gradually and continue to progress.

The majority of the diagnosed cases of TC in our community present lipoma of the filum terminale (fatty filum). We know of 1 case of diagnosed Occult Tethered Cord. [7]

At the present time, we are aware of 21 ZARD patients who have had surgical detethering of the spinal cord, all of which have reported improvement of some or all of the above listed symptoms (with the halting of progression of scoliosis and bladder dysfunction as the most frequently reported improvements).

It is interesting to note that in young children with ZARD who did not present clinical features of tethered cord but underwent detethering of the spinal cord (based on diagnostic imaging), some of the classic features of ZARD didn't develop later in life or developed with a milder presentation (such as: scoliosis, urine retention, urinary and/or fecal continence, pain in lower limbs, elevated tone, decreased range of motion in pelvis and lower limbs, decreased tactile feeling in lower limbs). All these cases were younger than 5 years of age at the time of surgical detethering.

Although as commented here, there are no studies on tethered cord in ZARD till date, it should be noted that previous studies have shown that in mouse and zebrafish embryos, the ZC4H2 protein is expressed in the brain and spinal cord and that its expression decreases in these areas with age.[4,5]
In addition, Kim et al.,[6] showed that *Zc4h2* plays a crucial role in the development of the embryonic neural tube in mice through cooperative involvement in the patterning of progenitor domains within the ventral spinal cord. These authors suggest an important role of ZC4H2 in brain and neural tube development. Spinal cord abnormalities as observed in ZARD patients could therefore have an embryonic origin.

We recognize the presence of (symptomatic) tethered cord in patients with ZARD and strongly recommend our community for timely screening and adequate medical/surgical intervention, especially in the presence of clinical symptoms related to it.

We attribute these conclusions to both the available literature, as cited in this statement, as well as to anecdotal evidence within our global community of diagnosed ZARD patients.

References:

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