Allegato 01 – Protocollo di studio

"Expanding phenotype of Wiedemann-Steiner Syndrome: C2-C3 vertebral fusion"

Summary
Wiedemann-Steiner syndrome (WDSTS) is a rare autosomal dominant disorder, resulting from mutations KMT2A gene, on the long arm of chromosome 11, mostly de novo. KMT2A (or mixed-lineage leukemia MLL) encodes a histone metyltransferase forming part of the epigenetic machinery and playing a key role in gene expression control during development (Lebrun et al. 2018).

WDSTS (OMIM 605130), originally characterized in 1989 by Wiedemann et al. (Wiedemann et al., 1989) and later in 2000 by Steiner et al. (Steiner et al., 2000), has since been described only a few times in the literature, with the phenotypic spectrum both expanding and becoming more delineated with each patient reported. WDSTS is mainly characterized by pre and post-natal growth retardation, adult short stature, feeding problems, psychomotor delay, intellectual disability, hypertricosis cubiti and distinctive facial features, including round and flat face, thick eyebrows, long eyelashes, dawn-slanting and vertically narrow palpebral fissures, widely space eyes, broad nasal bridge, wide nasal tip, low-set ears, long philtrum, high arched palate, dental abnormalities (Aggarwal et al. 2017). Over time other clinical features such as ocular abnormalities or strabismus, congenital immunodeficiency with recurrent infections of genitourinary tract or respiratory tract, kidney and cardiological malformations have been reported, expanding WDSTS phenotype (Stellaci et al. 2016, Storm et al. 2014, Sun et al. 2017).

Regarding skeletal features, delayed bone age, hip dysplasia, short limbs, short hands and foot, short fingers, 5th finger clinodactyly have been described in patients with WDSTS.

Recently, we detected an heterozygous variant of KMT2A (NM_005933.3:c.2513G>A;p.Trp838*) in a patient of our Clinical Genetics Unit, who has been investigated through exome sequencing. This variant has been predicted as pathogenic and the patient presents almost all typical clinical signs of WDSTS. The consensus phenotype includes

Our patient shows also C2-C3 vertebral fusion and foramen magnum stenosis. Recently, Leburn and colleagues (Leburn et al. 2018), described a patient carrying a missense variant of KMT2A and concording with WDSTS phenotype, who shows also C2-C3 vertebral fusion. In the literature this kind of skeletal anomaly has not been previously reported as phenotypic tract of WDSTS.

Despite what described in the literature, C2-C3 vertebral fusion seems to be rather present in patients with WDSTS, as we have known through the help of WDSTS family association. This suggest us the need to collect clinical data of patients with WDSTS and C2-C3 vertebral fusion, in order to insert this data in the management and follow-up of patients with WDSTS.

Objectives
The aim of the work is to affirm that C2-C3 vertebral fusion is one of the feature to investigate in patients with WDSTS, expanding WDSTS phenotype. For that, we will ask the collaboration of national and international colleagues and of family association in order to collect the clinical data of patients with WDSTS and C2-C3 vertebral fusion. These data will allow specialists to appropriately take care of patients with WDSTS (adding cervical X-ray in their clinical practice) and orient themselves towards optimal care measures (brain and spinal cord MRI, neurosurgery).

Patients selection

The project is addressed to all families of individuals affected by WDSTS, as well as their pediatricians and medical doctors. Inclusion criteria are the diagnosis of WDSTS and molecular confirmation of KMT2A gene alteration.

Study

The study will be a retrospective collection of clinical data and X-Ray imaging of patients with WDSTS.
In the first 3 months we will collect clinical and molecular data of patients with WDSTS and C2-C3 vertebral fusion, sending a proforma table to colleagues who take care of patients with WDSTS or directly to WDSTS family associations. The proforma table will enclose all molecular and clinical data about known typical features of WDSTS and information about C2-C3 vertebral fusion, its evolution and clinical or instrumental investigations required about it. Then we will ask also to send us cervical X-Ray and brain MRI of patients enrolled, if available.
In the second 3 months, we will compare data collected and we will check radiological findings with the help of colleagues with expertise in radiology. All data will be collected and analyzed by Dr. Ivanovski Ivan and Dr Caraffi Stefano Giuseppe.
Data regarding the evolution of C2-C3 vertebral fusion and its management will be used to draft guidelines about the follow-up of this anomaly in patients with WDSTS.

Publication and acknowledgement Policy

The results will be published on peer-reviewed journals, reporting all data in anonymous form in accordance with the informed consent provided by the patients' families. Colleagues, patients' families and family association will be properly acknowledged in any communication or publication for their support and collaboration.

References

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