C syndrome - what do we know and what could the future hold?

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In 1969 Opitz et al. {Opitz, 1969 #184} described two siblings with a new syndrome, which they called "C syndrome of multiple congenital abnormalities" and was presented as a "probably private syndrome". After this first description, new cases appeared with highly similar phenotypes and a new syndrome, known as C Syndrome, Opitz C Syndrome or Opitz Trigonocephaly Syndrome (OCS; MIM # 211750) was firmly established {Preus, 1975 #682;Oberklaid, 1975 #23;Antley, 1981 #159}.

OCS is clinically very variable, with a broad range of severity. It is characterized by developmental delay that is usually severe (but some cases with mild to normal intellect have been reported {Antley, 1981 #159;Lalatta, 1990 #87;Stratton, 1990 #694}). Trigonocephaly (due to the premature fusion of the metopic suture) is one of its main characteristics and, while it is not exclusive, it has become mandatory and definitional of OCS. The syndrome is also characterized by a particular set of facial dysmorphisms including an atypical nose (short, with a broad nasal bridge, micro- o retrognatia), anomalies of the eyes (hypotelorism or hypertelorism, thick epicanthic folds, strabismus, proptosis) and many of these anomalies might be attributed to the trigonocephalic ''sequence''. More specific of OCS are the oral anomalies commonly present in OCS patients, with alterations of the upper lip and philtrum, broad alveolar ridges with rugose anterior palatal mucosa, high arched palates and tooth malposition that may lead to mastication problems and feeding difficulties. Auricles are often low set, posteriorly angulated, and with abnormal helix and the neck is usually short and with redundant skin. Shortening of the limbs (especially rhizomelic and acromelic segments) and hypermobility of the joints are also common traits, together with polydactyly, and syndactyly. Some deformities of the trunk, including scoliosis, kyphosis, short or prominent sternum, widely spaced nipples and slender ribs are usually observed. Hypotonia, sometimes even in combination with hypertonia, and contractures, are also frequent, together with flexion deformities, especially in hands and feet. A variety of internal anomalies are also common, especially cardiac defects (present

in one half of OCS cases). Abnormal lobulations of the lungs and kidneys or malformations of the pancreas or liver are frequently reported. Many of the patients presented seizures at some point of their lives. Usually, the pregnancies go without complications, but sometimes anhydramnios due to renal anomalies or some of the most severe congenital anomalies could be detected by ultrasonography {Antley, 1981 #159;Zampino, 1997 #13;Bohring, 1999 #12;Opitz, 2006 #4}. CNS malformations (agenesis of the corpus callosum, cerebellar atrophy and Dandy-Walker malformation among others) are common, and, as has been pointed out previously {Zampino, 1997 #13}, all suggest that OCS represents a developmental defect of the cerebral midline. While none of the traits are obligatory (with the probable exception of trigonocephaly or prominent metopic suture) a combination of them should be present to represent the Opitz C clinical entity {Opitz, 2006 #4}.

Since 1969, some 60 cases have been reported in the literature {Opitz, 1969 #184;Preus, 1975 #682;Oberklaid, 1975 #23;Antley, 1981 #159;Flatz, 1984 #688;Sargent, 1985 #689;Fryns, 1985 #22;Preus, 1986 #691;Lalatta, 1990 #87;Stratton, 1990 #694;Camera, 1990 #717;De Koster, 1990 #718;Haaf, 1991 #20;Choudhury, 1992 #696;Schaap, 1992 #18;Chu, 1994 #725;Glickstein, 1995 #695;Sabry, 1997 #714;Omran, 1997 #14;Zampino, 1997 #13;McGaughran, 2000 #27;Weber, 2000 #722;Nacarkucuk, 2003 #723;Czako, 2004 #7;Yatsenko, 2005 #6;Chinen, 2006 #5;Opitz, 2006 #4;Kaname, 2007 #109;Travan, 2011 #2;Pokale, 2014 #727;Urreizti, 2016 #550;Pena-Padilla, 2017 #444;Urreizti, 2017 #549;Urreizti, 2018 #598} but they seem to represent a heterogeneous grouping. First, some cases carry chromosomal abnormalities, in chromosome 3 (del 3q {Sargent, 1985 #21}, rec(3) {Preus, 1986 #691}, 3p trisomy {McGaughran, 2000 #27}) or involving other chromosomes such as t(13;18)(q22;q23 {Chu, 1994 #725}, reciprocal translocation t(2;17)(p25;q24) {Czako, 2004 #7}, 13q22-qter partial trisomy {Phadke, 2004 #739}, 9q deletions {Yatsenko, 2005 #6}, reciprocal translocation t(3;18)(q13.13;q12.1) {Chinen, 2006 #5}, a deletion at 4q28.3q31.23 {de Ravel, 2009 #738} and der(7)t(7;13)(p22;q21) {Pokale, 2014 #727}. While these cases would not be considered as simple OCS, there could be putative genes related to OCS pathology in these chromosomal regions. In this sense, the 9q34.3 deletion first described in an OCS patient, has been identified as a microdeletion syndrome known as

Kleefstra Syndrome {Kleefstra, 2009 #733}, with some clinical overlap with OCS. Second, it has to be taken into account that, while trigonocephaly is one of the main characteristics of the OCS and it is a definitional trait, it is a common trait present in many other syndromes, including terminal deletions at 3p, 9p and 11q and in the distal 3q trisomy {McGaughran, 2000 #27}.

The relatively broad clinical spectrum of OCS overlaps other clinical entities and some patients initially considered as OCS have been finally re-diagnosed to other syndromes such as the Kleefstra Syndrome mentioned previously, Varady Syndrome or Kabuki syndrome {Say, 1981 #692;Cleper, 1993 #16;Sabry, 1997 #714;David, 2004 #724;Yatsenko, 2005 #6}. In 1999, a new syndrome highly overlapping OCS but with a more severe outcome was delineated. This C-like syndrome or Bohring-Opitz Syndrome (BOS, MIM # 605039) is clinically -and genetically- more homogeneous and it is mainly characterized by trigonocephaly (and microcephaly), nevus simplex (flammeus), intrauterine growth retardation (IUGR), failure to thrive, severe to profound developmental delay and characteristic fixed flexions of the elbows, wrists and metacarpophalangeal joints, known as BOS posture {Russell, 2015 #226}. BOS is mainly due to mutations in the *ASXL1* gene {Hoischen, 2011 #25;Magini, 2012 #76;Russell, 2015 #226}. In near one third of the patients fitting a typical clinical BOS phenotype no mutations in *ASXL1* can be detected, suggesting that it is a heterogeneous entity. In this sense, mutations in *ASXL3* {Bainbridge, 2013 #111}; *ASXL2* {Shashi, 2017 #728} and *KLHL7* {Bruel, 2017 #730} have been identified in patients clinically overlapping BOS.

The first gene associated with OCS was *CD96* (in chromosome 3q) {Kaname, 2007 #109}, found truncated in a patient diagnosed as OCS who bore a balanced translocation t(3;18)(q13.13;q12.1). These authors also identified a missense mutation in *CD96* in a patient diagnosed as BOS and demonstrated loss of adhesion and growth activities *in vitro* in cells with mutated *CD96*. While this gene plays a crucial role in inhibiting NK cells, in immune regulation and in surveillance {Georgiev, 2018 #731}, its role in OCS has been questioned. Firstly, Darlow et al {Darlow, 2013 #115} identified a t(2;3) balanced translocation disrupting *CD96* in patients who developed renal cell carcinoma without any symptoms of OCS. Secondly, in a study involving 10 OCS patients, no mutations in *CD96* could be identified {Urreizti, 2016 #550}. Finally, the *Cd96*−/− mice do not present any

neurodevelopmental phenotype and are, mainly, phenotypically normal {Chan, 2014 #732}. While the *CD96* deficiency could be playing some role in the presentation of the patient described by Kaname et al. it doesn't seem to be responsible for the disease. Interestingly, the *ASXL3* gene maps close to Kaname's patient break point at 18q12.1, and thus, could be the real cause of the disease in this patient.

Recent studies have identified two heterozygous mutations in the *IFT140* gene in one patient diagnosed as OCS {Pena-Padilla, 2017 #444}. Both mutations would lead to the loss of the functional protein (initiation codon loss and splice site mutation). This gene is associated with short-rib thoracic dysplasia 9 with or without polydactyly (SRTD9; MIM # 266920), a ciliopathy associated with skeletal and renal dysplasia, retinal pigmentary dystrophy and cerebellar ataxia. Polydactyly is also a common trait for these patients. These authors suggested that many of the OCS symptoms overlap with those of a cilliopathy, including dysplasia of kidneys, liver and pancreas with cystic changes, as well as some of the skeletal anomalies observed in some OCS patients, and highlight that retinitis pigmentosa, together with Caroli's syndrome and renal failure, was also previously described in another OCS patient {Weber, 2000 #722}.

Recent works have also identified heterozygous mutations in *MAGEL2* {Urreizti, 2017 #549} and *FOXP1* {Urreizti, 2018 #598} in 2 patients with initial diagnoses of OCS. *MAGEL2*-truncating mutations have been associated with a new syndrome described in 2013 {Schaaf, 2013 #258}, known as Schaaf-Yang Syndrome (SYS, MIM # 615547) and also with severe arthrogryposis {Mejlachowicz, 2015 #256}. SYS displays significant clinical overlap with OCS, including severe developmental delay, hypotonia, seizures, feeding problems in infancy and arthrogryposis or joint contractures and the fact that some patients presented with trigonocephaly or a prominent metopic suture. In contrast, the patient (MG) presented with thick palatal and alveolar ridges and multiple dislocations, more typical of OCS, and these features were absent in all the other SYS patients described, including those bearing the exact same mutation as that of patient MG. *MAGEL2* truncating mutations have been also found in patients diagnosed as Chitayat-Hall Syndrome {Jobling, 2018 #753}, characterized by distal arthrogryposis with hypopituitarism including growth hormone deficiency, intellectual disability, and facial anomalies, also common features in SYS, highlighting the broad clinical spectrum and overlap

of these syndromes. Heterozygous mutations in *FOXP1* have been associated with intellectual disability (ID) with language delay, with or without autistic features (MIM #613670). The FOXP1 Syndrome patients presented with intellectual disability (ID) with speech and language impairment and autism spectrum disorders (ASD). They also presented with some facial dysmorphisms including hypertelorism, strabismus, high-arched palate, short stature and enuresis, and thus, displaying some overlap with OCS. In this case, hitherto the patient initially diagnosed as OCS is the only FOXP1 syndrome patient presenting with true trigonocephaly, and thus, it is unclear if this condition is due to the *FOXP1* mutation or to another unknown condition present in this patient. In fact, the OCS phenotype of this patient was very apparent during early childhood, but it has been reconsidered after his development, a common fact among other "OCS patients".

Unlike the relatively genetically homogeneous BOS syndrome, OCS appears to be an extremely heterogeneous entity, and somehow, a "private syndrome" for each patient, as first postulated by Opitz et al {Opitz, 1969 #184}. It is evident now that there is no common genetic cause for OCS and in fact, some authors have declared it "extinct" {Toriello, 2016 #736}. It is clear that it cannot be considered an "autosomal recessive disorder" any more, as other inheritance patterns have been observed, mainly the *de novo* dominant pattern. This has to be taken into account during genetic counseling as the risk of recurrence is unknown until a molecular diagnosis is achieved. In our opinion, OCS still represents a useful clinical description that summarizes a constellation of symptoms helping clinicians and geneticists to narrow the clinical spectrum of the patient, helping in the difficult task of the diagnosis of severe neurodevelopmental disorders (NDD). Nowadays, whole exome sequencing (WES) is a powerful tool that will allow to identify the molecular basis of most (if not all) of the cases initially diagnosed with the OCS phenotype, as has been achieved in the 3 last cases previously mentioned, and thus, to re-diagnose each patient according with the particular molecular cause of the disease. The OCS phenotype also helps to highlight their particularities, as the thick palatal and alveolar ridges or the multiple dislocations in the *MAGEL2* patient and the trigonocephaly in the *FOXP1* patient diagnosed by us. Finally, the OCS clinical "label" helps also the patients and their families to navigate during the diagnosis odyssey that usually represents their early lives,

giving the families the solace of a name to an unknown condition, in contrast with the "unknown" label that is usually extremely stressful for these families.

In this context, it is obvious that there is no option to a global OCS therapy right now. So far the only approaches are the surgical correction of the trigonocephaly and internal anomalies such as cardiovascular malformations, and symptomatic treatment as in the case of seizures. In each case, the identification of the molecular cause of the disease opens a door to particular therapeutic strategies, such as the undergoing clinical trials on Oxytocin treatment for SYS patients and their treatment with growth hormone, as has been suggested {Jobling, 2018 #753; McCarthy, 2018 #746}. As *MAGEL2* is a maternally silenced gene enclosed in the Prader-Willy chromosomal region, one could hypothesize that reactivation of the maternal allele could be a therapeutic strategy, as has been shown for other genes of the PW region {Kim, 2017 #486}. The main challenge now is to improve our knowledge on the molecular basis of OCS. Functional studies would be necessary to stablish if the OCS associated mutations represent loss or gain of function and to identify common functional denominators and converging pathways that could be the target of orphan drugs. Mutations have specific downstream consequences that may account for the majority of the pathogenic burden and can be the target of common therapeutic strategies. In addition, there is a strong link between development and cancer {Bellacosa, 2013 #420}. So far, *FOXP1*, *ASXL1*, *ASXL2* and *ASXL3*, all related to OCS, BOS or similar clinical entities, have been found involved in cancer development or malignancy {Daou, 2018 #775; De Silva, 2019 #774}. This relationship makes it possible to take advantage of the knowledge obtained from cancer research, and may open a door to the use of cancer drugs in neurodevelopmental diseases. In this sense, drug repurposing is a promising and affordable option in extremely rare diseases such as OCS and related syndromes and is starting to be a reality in other rare diseases as in the case of Arimoclomol, a candidate drug to treat insulin resistance {Kurthy, 2002 #779} and granted orphan drug designation for multiple lysosomal storage disorders including Niemann-Pick disease type C (ClinicalTrials.gov, identifier NCT02612129) {Kirkegaard, 2016 #77} and Gaucher Disease {Fog, 2018 #778}. The Arimoclomol effect as a Heat Shock Protein (HSP)-modulating drug (particularly HSP70) makes it suitable as a therapeutic agent in more than one particular LSD. At present, a better knowledge of the bases of OCS is a

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necessary first step towards finding an appropriate therapeutic strategy for these diseases.

References:

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