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Early fetal presentation of Koolen-de Vries: Case report with literature review

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A B S T R A C T

Koolen-de Vries syndrome (MIM#610443) is a rare microdeletion syndrome involving the 17q21.31 region, which was first described by Koolen in 2006. Clinical and behavioral characteristics have been extensively reported from more than 100 postnatal cases including infants, children and young adults. The syndrome is highly clinically heterogeneous, but the main features associate characteristic craniofacial dysmorphism, heart defects, limb, skeletal, genito-urinary anomalies, along with intellectual disability with early childhood epilepsy and behavioral disturbances. Central nervous system malformations usually consist in hydrocephalus and thin corpus callosum. We report herein an early fetal case with an apparently isolated abnormal corpus callosum diagnosed by ultrasonography, for which a medical termination of the pregnancy was achieved at 22 weeks of gestation. Postmortem examination displayed facial dysmorphism consisting of hypertelorism, short philtrum and flat and broad nose, cleft palate and left duplex ureter. Neuropathological examination revealed a mega corpus callosum that has never been reported so far in this syndrome. Array-CGH performed on thymic DNA tissue revealed a 17q21.31 microdeletion, which allowed for the confirmation of early occurring Koolen-de Vries syndrome.

1. Introduction

Koolen-de Vries syndrome (MIM#610443) is a rare but probably underdiagnosed microdeletion syndrome involving the 17q21.31 region, which was first described by Koolen and de Vries in 2006, testing 360 mentally retarded individuals obtained from a European collaborative work. Its incidence has been estimated at 1:16,000 in the general population (Koolen et al., 2008). The deletion which occurs mainly *de novo* results from non-allelic homologous recombination between low copy repeats and spans about 500 kb (Egloff et al., 2014; Terrone et al., 2012), a region containing at least 6 genes including *C17orf69, CRHR1, SPPL2C, MAPT, STH and KANSL1* (KAT8 regulatory NSL complex subunit 1). It has been shown that haploinsufficiency of *KANSL1*gene, a regulator of chromosome modification, is sufficient to cause the 17q21.31 microdeletion syndrome phenotype (Koolen et al., 2012a; Zollino et al., 2012). Importantly, *KANSL1* gene may also be altered by point mutations responsible for a phenotype close to that observed in Koolen-de Vries syndrome (Zollino et al., 2012). Currently, clinical and behavioral characteristics have been extensively reported from more than 100 postnatal cases including infants, children and young adults. The syndrome is highly variable, but clinical features encompass a variety of abnormalities including a relatively characteristic craniofacial dysmorphism as well as heart (atrial and/or ventricular septal defects), limb, skeletal and genito-urinary anomalies. Besides, patients generally present with low birth weight, neonatal hypotonia, developmental delay, intellectual disability with early childhood epilepsy, poorly developed language, poor feeding and behavioral disturbances consisting in either hypersociability reminiscent of Angelman and Williams syndromes (MIM#608146 and MIM#612546 respectively) or bad humor and poor interaction with other children (Egger et al., 2013). Central nervous system (CNS) malformations usually consist in hydrocephalus and thin corpus callosum (Koolen et al., 2008). To our knowledge, a single fetal case with neuropathological examination has been reported so far (Egloff et al., 2014). This study aims at describing a second fetal case displaying other severe CNS abnormalities revealed by routine ultrasonography at 20 WG and confirmed by post-mortem examination.

2. Clinical report

2.1. Case history

A thirty-five-year-old woman, gravida 2 para 1 underwent routine ultrasound (US) examination at 10 weeks of gestation (WG), which was considered as normal. Routine US examination performed at 20 WG revealed cleft palate, mitral focus and dysgenesis of the corpus callosum with no associated brain abnormalities, in particular regarding fetal brain development (Fig. 1A and B, control case for comparison). The discovery of this malformative complex led to medical termination of the pregnancy, which was achieved at 22 WG, in accordance with French law and after approval of our local ethical committee. The unrelated parents had no personal or familial medical history.

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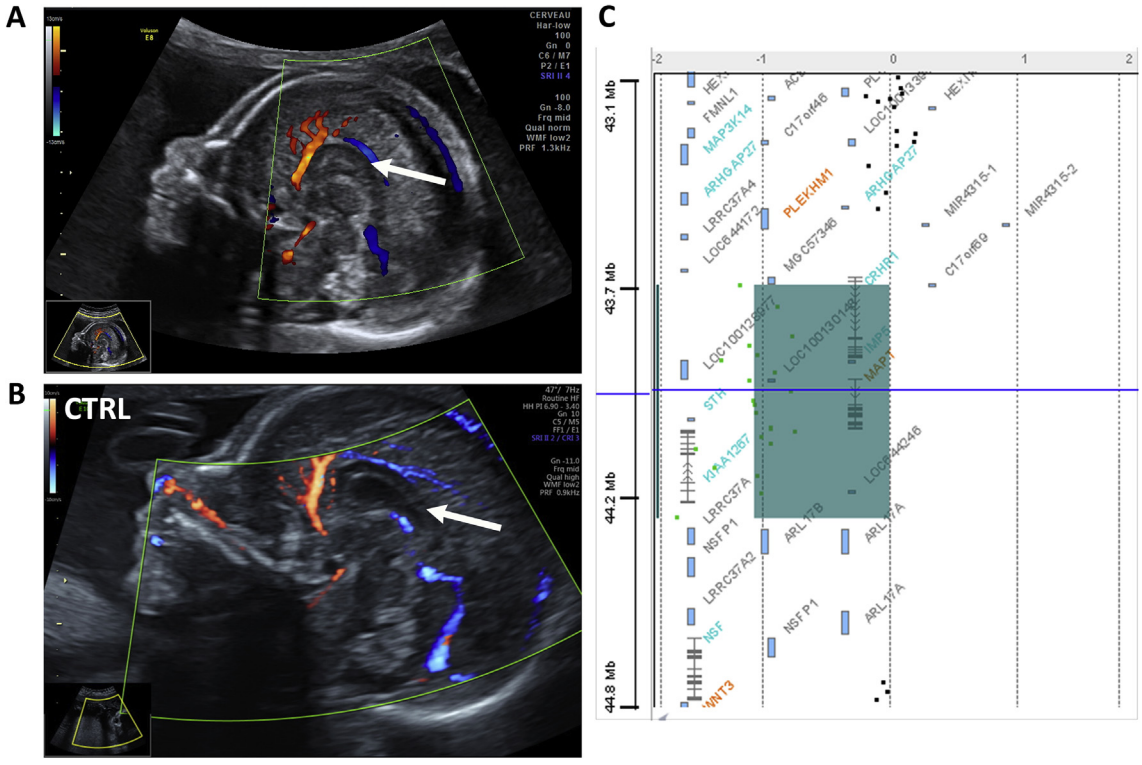

Fig. 1. Brain ultrasound of the fetus and array-CGH profile.
A: Brain ultrasound of the patient at 20 WG, displaying an abnormally short (white arrow) and mega corpus callosum, but with no other identifiable lesion, apart from verticalization of the anterior cerebral arteries.
B: compared to an age matched control, where the corpus callosum is thinner and longer (white arrow), with normal positioning of the anterior cerebral arteries.
C: Array-CGH profile (from Genomic Workbench Lite Edition 6.5 software), hybridized against a "reference" DNA, showing the chromosomal region 17q21.31. Each dot represents an oligonucleotide probe and the results are expressed in log2 ratio: a log2 ratio around −1 represents a deletion of the corresponding genomic region (green dots), whereas a log2 ratio around 0 corresponds to 2 copies of the corresponding genomic region (black dots). Genes of the region are also shown in the figure: *KIAA1267* is the alternative name of *KANSL1, IMP5* is the alternative name of *SPPL2C*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.2. Cytogenetic investigations

Oligonucleotides array-CGH was performed using 8*60K whole genome microarrays (Agilent Technologies, Santa Clara, California) according to manufacturer's instructions, after DNA extraction from fetal thymic tissue using standardized procedures. Fetal DNA was analyzed by means of comparative genomic hybridization with fluorochrome swapping; in a trio along with DNA from two patients displaying another phenotype. Fluorescence ratio was calculated to detect chromosomal imbalances. Deletions and duplications were taken into consideration when a minimum of three consecutive variant points was detected by the statistical algorithm ADM-2 with a threshold of 5 (Agilent Genomic Workbench Lite Edition 6.5, Agilent Technologies, Santa Clara, California).

Array-CGH made it possible to identify a deletion in 17q21.31 with a minimal size of 627 kb (chr17:43,717,703–44,345,038), and a maximal size of 1274 kb (chr17:43,513,427.44,787,865) (Hg19). This deletion included at minimum 5 RefSeqs genes (*KANSL1*, *CRHR1*, *SPPL2C*, *MAPT* and *STH*), corresponding to the recurrent microdeletion syndrome called Koolen-de Vries syndrome (OMIM#610443) (Fig. 1C).

Parental DNA studies performed by 8*60K array-CGH showed that the deletion occurred *de novo* in the fetus.

2.3. General autopsy findings

A complete autopsy was performed with the informed written consent of the parents and following standardized protocols including X-rays, photographs, macroscopical and microscopical examination of all viscera. The male fetus weighed 614 g (50th centile). External examination confirmed posterior cleft palate and disclosed cranio-facial dysmorphism consisting of hypertelorism (20 mm between inner canthus for 47 mm between outer canthus), flattened nose with broad nasal ridge, bulbous tip and anteverted nostrils, short philtrum, thick lips (Fig. 2A), flat face with apparently

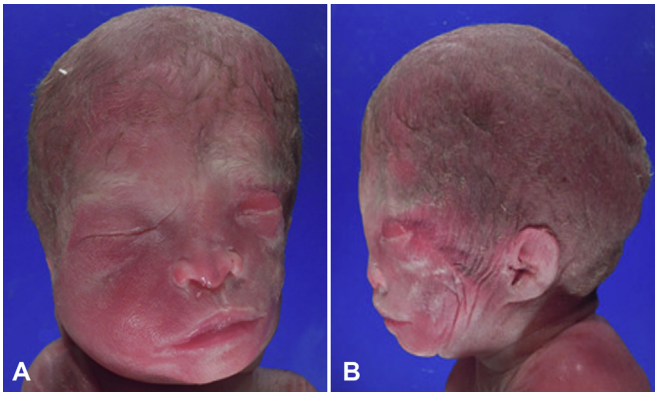

Fig. 2. External presentation of the fetus.
A: Frontal view showing cranio-facial dysmorphism consisting of hypertelorism, broad and flattened nose with bulbous tip and anteverted nostrils, short philtrum and thick lips.
B: Left profile of the fetus face showing flat face with microretrognathism and low set and large ears.

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