

**CASE REPORT****Cerebro–fronto–facial syndrome (Dandy-Walker Variant and Frontofacial Dysmorphisms): report of the first case identified by increased nuchal translucency beyond 13<sup>+6</sup> weeks**Gabriele Tonni<sup>1</sup>, Daniela Azzoni<sup>1</sup>, Fabrizio Ambrosetti<sup>2</sup>, Claudio de Felice<sup>3</sup>, and Alessandro Ventura<sup>1</sup><sup>1</sup>Division of Obstetrics and Gynecology, Guastalla Provincial Hospital, AUSL Reggio Emilia, <sup>2</sup>Pathologic-Anatomy Service, 'Santa Maria Nuova' Hospital, Reggio Emilia, <sup>3</sup>Department of Neonatology, Policlinic Hospital 'Santa Maria alle Scotte', University of Siena, Italy

**ABSTRACT** A 32-year-old gravida 2, para 1 woman, with a previous uneventful pregnancy, underwent first trimester ultrasound screening for Down syndrome at 13 weeks according to the Fetal Medicine Foundation guidelines (<http://www.fetalmedicine.com/pdf/11-14/english/FMF-English.pdf>). The ultrasound showed increased nuchal translucency (NT) of 8.9 mm with an estimated risk of Down syndrome of 1:8. Fetal karyotype was normal 46,XX by chorionic villus sampling. The patient underwent weekly ultrasound and at 19 weeks of gestation, a dilatation of the 4th ventricle with partial agenesis of the cerebellar vermis and normal posterior fossa were observed by transvaginal transcerebellar section of the fetal head. This finding was consistent with a diagnosis of Dandy-Walker variant and the patient opted for termination of pregnancy after extensive counselling. Autoptic examination confirmed the prenatal ultrasonographic findings and revealed signs of an underlying cerebro–fronto–facial syndrome due to the presence of facial dysmorphisms consistent with horizontal eyelid, high nasal root, low set ears and a wide forehead. Increased NT is not only a common phenotypic expression of chromosomal abnormalities, but is also associated with a wide range of fetal defects and genetic syndromes. Careful ultrasonographic follow-up is mandatory in all cases of increased first trimester nuchal translucency with normal karyotype in order to identify associated anomalies.

**Key Words:** Dandy-Walker Variant, facial dysmorphism, genetic syndrome, increased nuchal translucency, ultrasound

**INTRODUCTION**

Classically, the Dandy-Walker complex has been divided into Dandy-Walker malformation (DWM), Dandy-Walker variant (DWV) and mega cisterna magna (MCM). Dandy-Walker malformation is characterized by a complete or partial agenesis of the cerebellar vermis with an associated enlarged posterior fossa. Dandy-Walker variant is classifiable into different grades of cerebellar vermis hypoplasia and cystic dilatation of the fourth ventricle, without enlargement of the posterior fossa. Mega-cisterna

magna is distinguished by an enlargement greater than 10 mm with integrity of both cerebellar vermis and fourth ventricle (Harwood-Nash & Fitz 1976; Pilu & Nicolaides 1999). Although Dandy-Walker malformation has an estimated prevalence of about 1:30 000 births, the incidence and the pathophysiology of Dandy-Walker variant and mega-cisterna magna are still unknown (Osenbach & Menezes 1991).

Dandy-Walker malformation may occur as an isolated finding (Murray *et al.* 1985) or as a part of Mendelian disorders such as achondrodysplasia (Souka *et al.* 2001), Walker-Warburg, Meckel-Gruber, Aicardi, Ellis-van Creveld or Fraser syndromes (Murray *et al.* 1985; Keogan *et al.* 1994); or chromosomal aberrations such as trisomy 18, 13 or trisomy 9 (Nyberg *et al.* 1991; Sepulveda *et al.* 2003). In the absence of a recognizable syndrome, an empiric recurrence risk of 1–5% may be suggested (Murray *et al.* 1985). Familial occurrence has also been reported and in rare cases the disease can be inherited as an autosomal recessive trait (Murray *et al.* 1985).

DWV may be associated with central nervous system (CNS) abnormalities including ventriculomegaly, agenesis of the corpus callosum, encephalocele, or in the cerebro–fronto–facial syndrome (OMIM 608578) (<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=608578&cmd>). This new syndrome was originally described by Guion-Almeida and Richieri-Costa (Guion-Almeida & Richieri-Costa 1992) in a Brazilian girl (born to nonconsanguineous parents) who had diffuse cortical atrophy associated with agenesis of corpus callosum as well as frontonasal dysostosis, abnormal upper lids, cleft lip/palate and redundant skin in the neck. The case was classified as an acrocallosal syndrome.

Another case was in a Brazilian girl, born to nonconsanguineous parents, with brachyacrocephaly, a wide forehead, wide palpebral fissures with multiple eyelid colobomas, a broad and high nasal root, ear anomalies and Dandy-walker anomaly with mental retardation (Guion-Almeida & Richieri-Costa 1999). Similar cases have also been reported recently in a Brazilian boy (Guion-Almeida & Richieri-Costa 2001) and in a Japanese girl. (Masuno *et al.* 2000).

Many reports have focused attention on the defects and syndromes associated with an increased nuchal translucency at 10–14 weeks of gestation in chromosomally normal fetuses (Bilardo *et al.* 1998; Souka *et al.* 1998, 2001; Tonni *et al.* 2005). Sherer *et al.* (Sherer *et al.* 2001) have reported a transvaginal diagnosis of DWM at 13 weeks gestation and Chen *et al.* (Chen *et al.* 2003) have described a DWM at 13 weeks gestation presenting with increased nuchal translucency and generalized edema that were associated with normal fetal karyotype.

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Received August 22, 2006; revised and accepted November 10, 2006.

A case of persistent increased nuchal translucency beyond 13<sup>+6</sup> weeks gestation associated with Dandy Walker variant and fronto-facial dysmorphism is reported.

## CASE REPORT

A 32-year-old G2P1, with a previous uneventful pregnancy, underwent first trimester ultrasound screening for Down syndrome at 13 weeks of gestation according to the Fetal Medicine Foundation guidelines (<http://www.fetalmedicine.com/pdf/11-14/english/FMF-English.pdf>). A nuchal translucency measuring 8.9 mm was observed using a 5 MHz transabdominal probe (Technos Esaote, Genoa, Italy) (Fig. 1). Particular attention was given in order to exclude a diagnosis of cystic hygroma and/or an underlying umbilical cord. The risk of Down syndrome was then calculated and resulted in a screen positive test of 1:8 (positive cut-off = 1:300). Fetal karyotyping by chorionic villus sampling was achieved after signed informed consent and resulted in a normal 46,XX. The patient underwent weekly scans demonstrating a persistent increased nuchal fluid beyond 13<sup>+6</sup> weeks evolving as a nuchal edema. At 19 weeks of gestation, a cystic dilatation of the 4th ventricle with partial agenesis of the cerebellar vermis and a normal posterior fossa were seen by targeted, transvaginal ultrasound neuroimaging of the fetal head (Fig. 2).

After extensive counselling, the patient opted for termination of the pregnancy which was achieved at 20 weeks of gestation by vaginal administration of prostaglandin E (Cervidil).

Autoptic examination confirmed the prenatal ultrasound findings of persistent second trimester (Fig. 3) nuchal fluid and documented the following: dilatation of the 4th ventricle without concomitant dilatation of the third, and agenesis of the cerebellar vermis with normal posterior fossa (Fig. 4). Fronto-facial dysmorphism were characterized by a wide forehead, horizontal palpebral rims, high nasal filter, high nasal root and low set ears (Fig 5a,b).

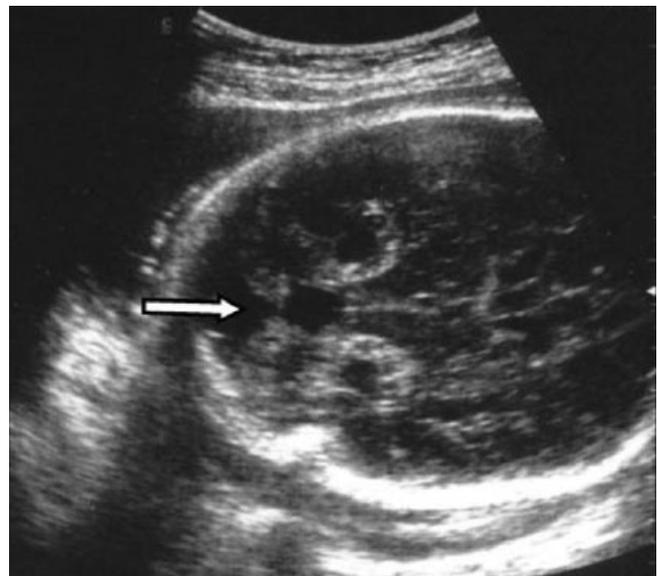
The heart underwent a thorough search with histological sections performed in the same way a 4-chamber view is obtained by fetal echocardiography. No congenital heart defects were diagnosed. No chest or abdominal abnormality were seen. Total-body X-ray did not demonstrate either skeletal or limb abnormalities.



**Fig. 1** Transvaginal scan of the embryo at week 13 in anterior spine position showing an increased nuchal translucency (NT) of 8.9 mm (white arrow).

## CONCLUSION

After a careful Medline examination of the English published works, this is the first report of a cerebro-fronto-facial (CFF) dysmorphism identified by a persistent increased nuchal translucency beyond 13<sup>+6</sup> weeks in a fetus with normal karyotype. Winter (Winter 2001) proposed that the patients described in the report by Guion-Almeida and Richieri-Costa (Guion-Almeida & Richieri-Costa 2001) represent a syndrome that has been called cerebro-fronto-facial syndrome. This syndrome is comprised of 3 types encompassing a spectrum of disorders with unique facial dysmorphism and brain abnormalities. Embryological studies have shown that the cerebellum starts to develop at the end of the embryonic period from the *alar plate* of both the isthmus and the first rhombencephalic neuromeres. The superior and inferior cerebellar peduncles are distinguishable at Carnegie stage 23, which corresponds to 27–31 mm of greatest embryonic length or approximately 56 postfertilization days. The development of the cerebellar vermis, formed from the median portion of the cerebellar hemispheres is completed at about week 17–18 (O’Rahilly & Muller 1999). It is known that a nuchal translucency >95–99th centile is associated with an increased incidence of chromosomal abnormalities and a variety of fetal malformations including cardiac defects, dysplasia and genetic syndromes (Souka *et al.* 1998, 2001; Atzei *et al.* 2005; Tonni *et al.* 2005). The associations between increased nuchal thickness and DWM have already been published (Bilardo *et al.* 1998; Souka *et al.* 2001; Chen *et al.* 2003) although there is still a lack in the explanation of the etiologic factors. A possible mechanism for the increased nuchal thickness in our case may be related to dilatation of the jugular lymphatic sacs, due to developmental failure in the connection with the venous system. Alternatively, a primary abnormal dilatation or proliferation of the lymphatic channels may have interfered with a normal flow between the lymphatic and venous systems. This may also explain the persistent increase in nuchal thickness beyond the 13<sup>+6</sup> weeks and its evolution into nuchal edema during the 2nd trimester.



**Fig. 2** Transvaginal transverse scan of the cephalic pole at week 19 showing a vermin defect, a cystic dilatation of the 4th ventricle together with a cisterna magna of normal size (white arrow).



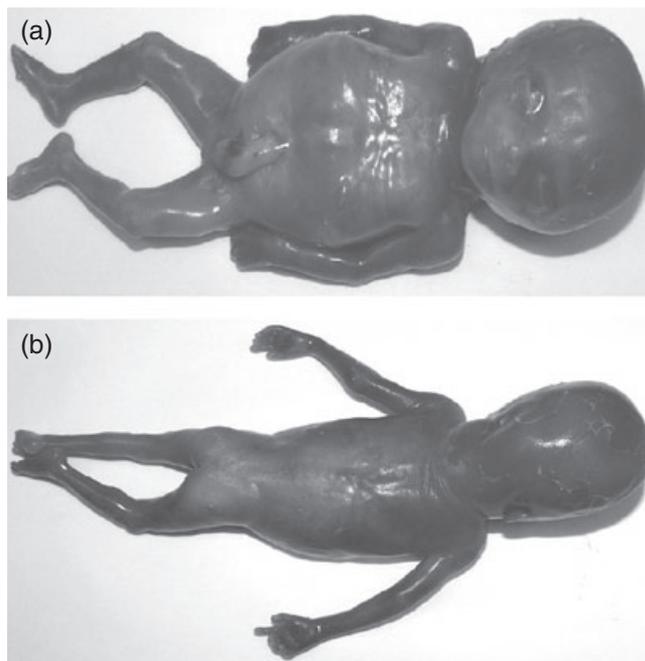
**Fig. 3** Macroscopic finding at autopsy showing an increased nuchal fold and the low set ear.

The diagnostic clusters of the CFF syndrome especially those involving the eyelid, the nose, the ear and the brain (DWV with dilated 4th ventricle and normal cisterna magna) were described by autopsy on the aborted fetus. A detailed examination of the fetal heart was performed with 'cuts' that resembled those used in the ultrasound study of the 4-chamber view. Congenital cardiac defects as well as thoraco-abdominal and/or musculoskeletal abnormalities were excluded.

The prenatal counselling was based on the following observations: (i) severely increased nuchal translucency in the first trimester associated with normal karyotype; (ii) weekly ultrasound follow-up showing persistent increased nuchal fluid beyond 13<sup>+6</sup> weeks' gestation evolving into nuchal edema; (iii) 2nd trimester 'targeted' transvaginal *neuroscan* enabling detection of absent cerebellar vermis and a dilated 4th ventricle with normal cisterna magna. Nevertheless, facial dysmorphisms went unnoticed during the 2nd trimester scan thus underlying the importance of autopsy examination in all cases of suspected or known fetal malformations. The outcome of fetuses affected by DWM and DWV may vary from severe mental and physical handicaps to normal neurodevelopment and function. Children with DWM and DWV who survive the neonatal period may later require ventriculo-peritoneal shunting for



**Fig. 4** Autoptic specimen showing absent vermian prominence with normal cisterna magna and enlargement of the 4th ventricle.



**Fig. 5** Autoptic specimen showing: (a) wide forehead, horizontal palpebral rims, high nasal filter with broad nasal root; (b) low set ear.

hydrocephalus. These children may demonstrate learning and/or motor deficits (Estroff *et al.* 1992; Chang *et al.* 1994; Keogan *et al.* 1994; Ecker *et al.* 2000). The worst prognoses are generally seen in cases with associated structural and chromosomal abnormalities while on the counterpart, isolated DWV has the highest chance of leading to normal neurodevelopment (Ecker *et al.* 2000).

Today in Italy, we are facing an increasing trend of parents wanting to have the 'perfect child' and although the fetus had a high chance of being cognitively normal, the couple opted for termination of the pregnancy. Mothers with positive, first trimester nuchal translucency tests, even if associated with normal karyotype should undergo a detailed ultrasound search for fetal malformations and echocardiography by expert sonographers. Implementation of *in*

uterine use of ultrasound plus MRI (magnetic resonance imaging) to integrate antenatal diagnosis is advocated in all cases of suspected or known fetal abnormalities, when possible. The more accurate the prenatal diagnosis, the more effective the prenatal counselling and thus the parental decision-making process.

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