Fetal Cerebral Ventricular Dilatation: Etiopathogenic Study of 130 Observations

Sihem Darouich *[1], Lucile Boutaud[2,3,4], Bettina Bessières[2], Maryse Bonnière[2], Jelena Martinovic[5], Charlotte Mechler[2], Caroline Alby[2,3], Jean-Pierre Bernard[6], Philippe Roth[6], Yves Ville[6], Valerie Malan[2,3,4], Michel Vekemans[2,3,4], Tania Attié-Bitach[2,3,4], and Férechté Encha-Razavi[2]

Background: Fetal cerebral ventricular dilatation (CVD) is a common abnormal prenatal finding that often predicts a poor prognosis. The etiology involves both genetic and nongenetic factors with diverse pathogenic mechanisms. We describe the neuropathological features of CVD in a large cohort of fetuses. The goals are to determine the physiopathological mechanisms and etiologies. **Methods:** We retrospectively analyzed a series of 130 fetuses examined at the Necker University Hospital following termination of pregnancy between January 2000 and December 2014. Chiari II and Dandy-Walker malformations were excluded from our study population. Karyotype and/or array comparative genomic hybridization were performed in all cases. Targeted Sanger sequencing or next generation sequencing were carried out in 34 and 5 cases, respectively. **Results:** We distinguished four groups of pathological entities: (1) midbrain/hindbrain patterning defects (54 cases, 42%), mainly related to aqueduct of Sylvius anomalies (atresia or stenosis); (2) cerebral cytoarchitectonic disorders (16 cases, 12%), essentially resulting from arachnoidal neuroglial ectopia; (3) hemorrhagic and perfusion failure (42 cases, 32%); and (4) nonspecific CVD (18 cases, 14%), without apparent obstruction, cortical malformation, or clastic injury. Although the pathogenic mechanisms of CVD were identified in 86% of cases, the causes, both acquired and genetic, were recognized in 21% of cases only. **Conclusion:** The neuropathological analysis is a powerful tool in the diagnosis of the fetal CVD pathogenic mechanisms and to identify homogeneous groups. The paucity of molecular diagnosis, notably in the major groups of midbrain/hindbrain patterning defects and hemorrhagic and perfusion failure, highlights the needs of future research to improve our current knowledge on CVD causes.

Birth Defects Research 00:000–000, 2017.

Key words: fetus; neuropathology; cerebral ventricular dilatation; hydrocephalus; central nervous system

Introduction

Background

- ✓ Cerebral ventricular dilatation: excess of cerebrospinal fluid
- ✓ Poor prognosis: cerebral and/or extracerebral malformations
- ✓ Challenging abnormality: need for a comprehensive classification and consensus

Objectives

- ✓ Etiopathogenic analysis of a series of fetuses with CVD in order to identify homogeneous groups of developmental disorders and to improve our current knowledge about this

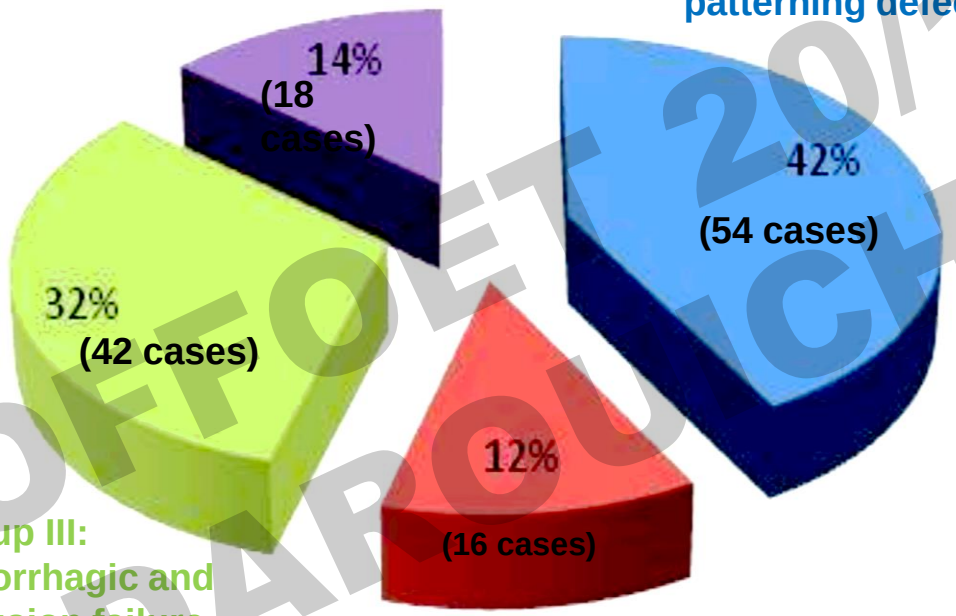
Materials and Methods

- ✓ 132 fetuses, from 12-41 WG with CVD, were identified from 2600 autopsy cases (5%) performed at the Necker University Hospital from January 2000 to December 2014
- ✓ 130 fetuses (129 families)
- ✓ Feto-neuropathological data, antenatal karyotype (114 cases) and array-based CGH (52 cases) results were provided in all cases
- ✓ Targeted Sanger sequencing was carried out in cases with clinically suspected conditions, such as L1 syndrome, porencephaly, peri-ventricular nodular heterotopia (PVNH), overgrowth syndrome, and osteochondysplasia
- ✓ Multi-gene panel testing (neuropathological alterations): O-glycosylation disorders, dorso-ventral polarization anomalies, corpus callosum abnormalities, tubulinopathies, ciliopathies.
- ✓ The NGS: few cases with familial recurrence, typical type II lissencephaly or L1 syndrome of yet unidentified gene, and L1 syndrome phenocopy in female fetuses

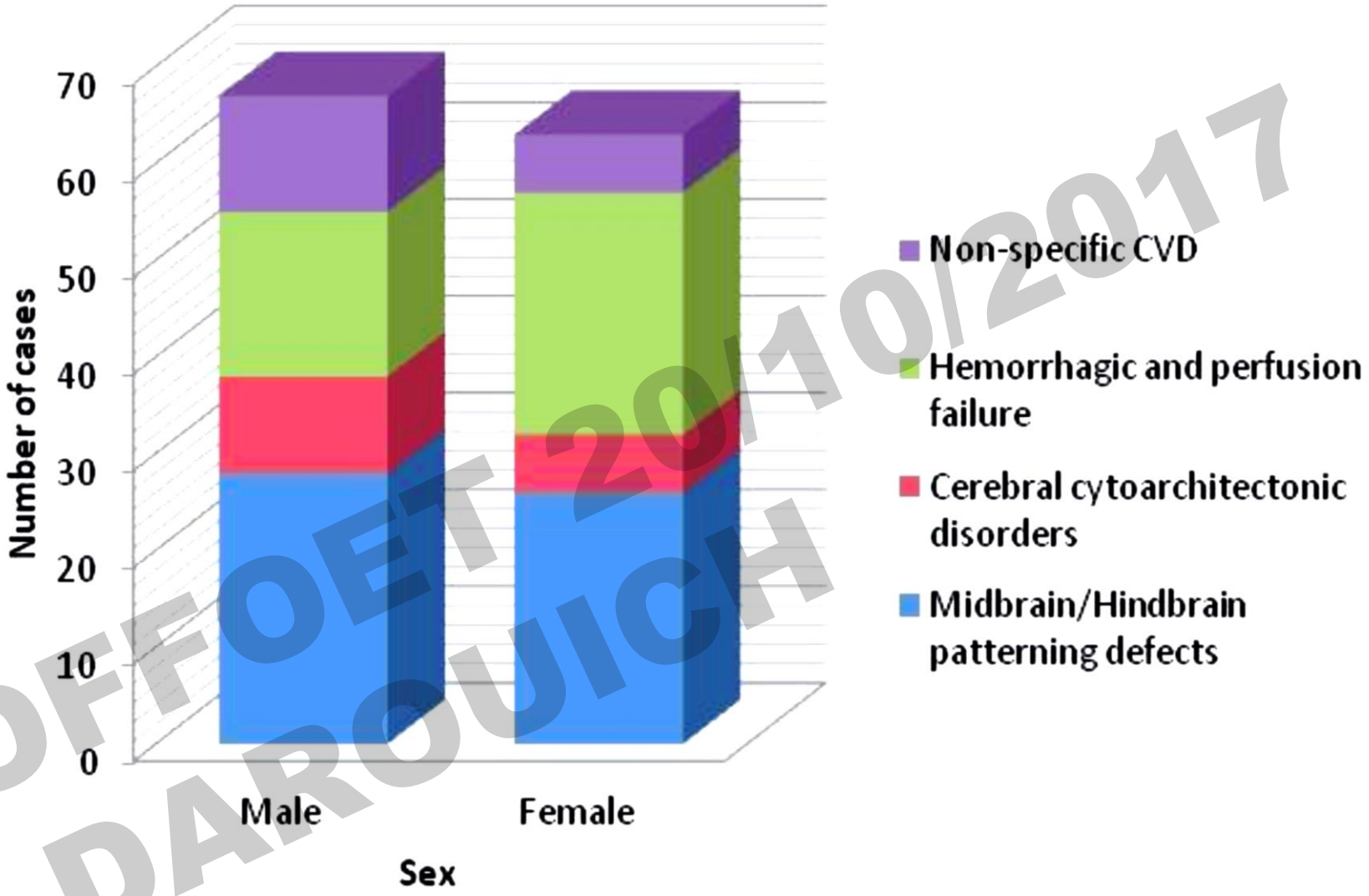
GENERAL AUTOPSY FINDINGS

- Sex ratio : 1.06
- The CVD was mainly detected in the second trimester of pregnancy (56 %)
- Macrocrania with suture disjunction (46 cases, 35 %)
- Dysmorphic facial features (68 cases, 52 %)
- Visceral malformations (heart defects, renal anomalies) and/or skeletal anomalies (59 cases, 45%)

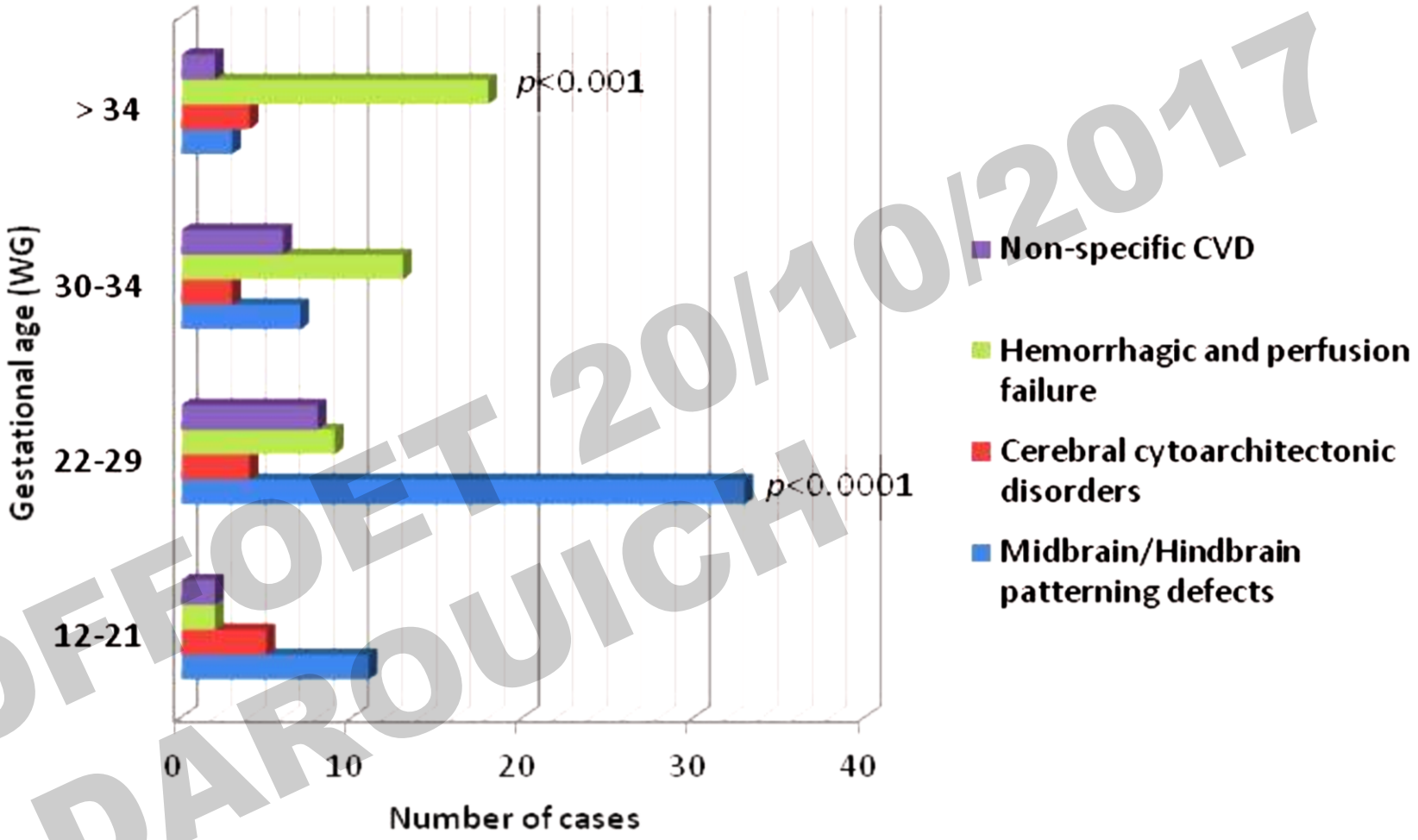
NEUROPATHOLOGICAL FINDINGS



- Group I: AS atresia and/or V3/AS stenosis
- Group II: Arachnoidal neuroglial ectopia /Other cytoarchitectural abnormalities
- Group III: Ex vacuo CVD/AS atresia due to gliotic scarring/Aqueductal obstruction by blood clot
- Group IV: Unexplained CVD

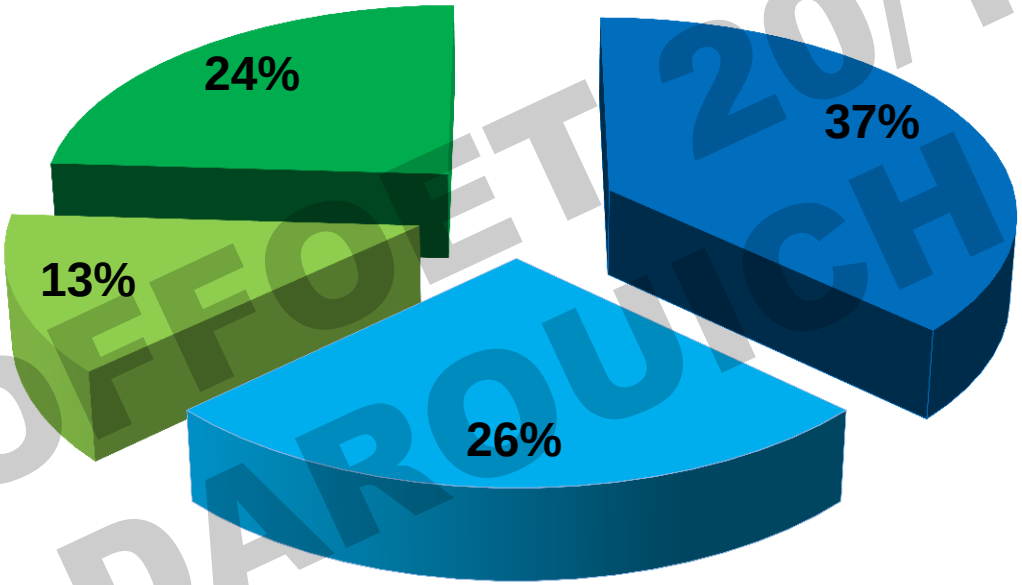


- The group II was associated with a male predominance (sex ratio: 1.6), whereas the group III was associated with a female predominance (sex ratio: 0.7)



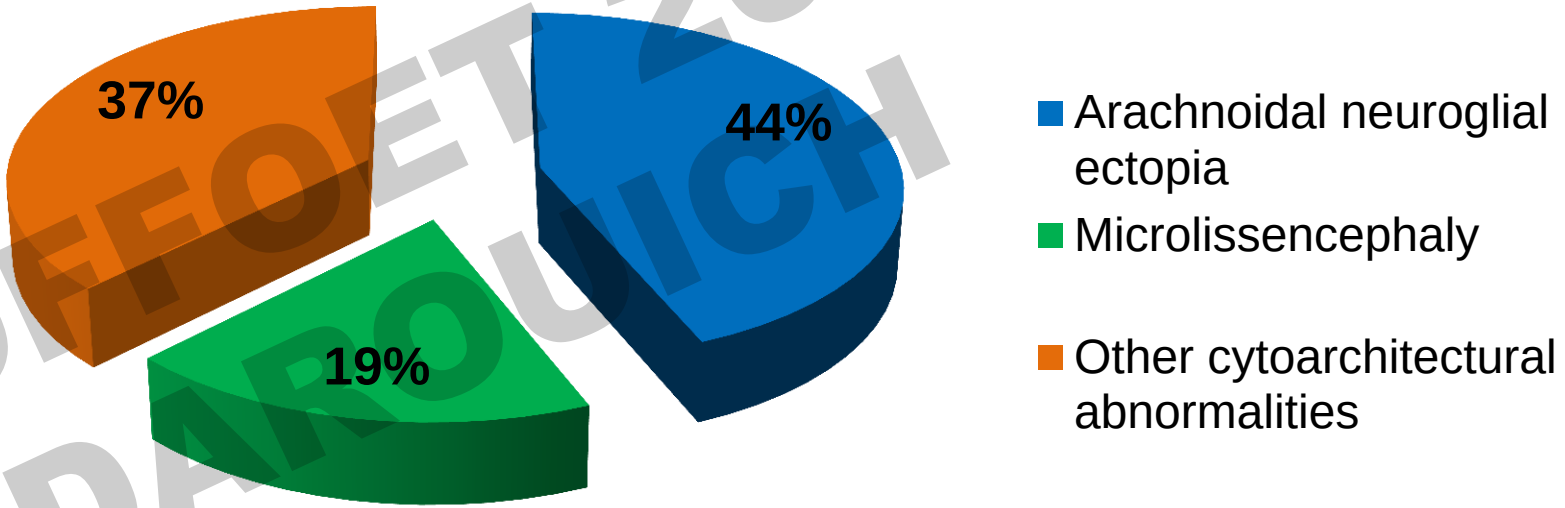
- The CVD was mainly detected in the second trimester of pregnancy in the groups I and II, and in the third trimester, especially after 34 WG, in the group III

GROUP I: MIDBRAIN/HINDBRAIN PATTERNING DEFECTS

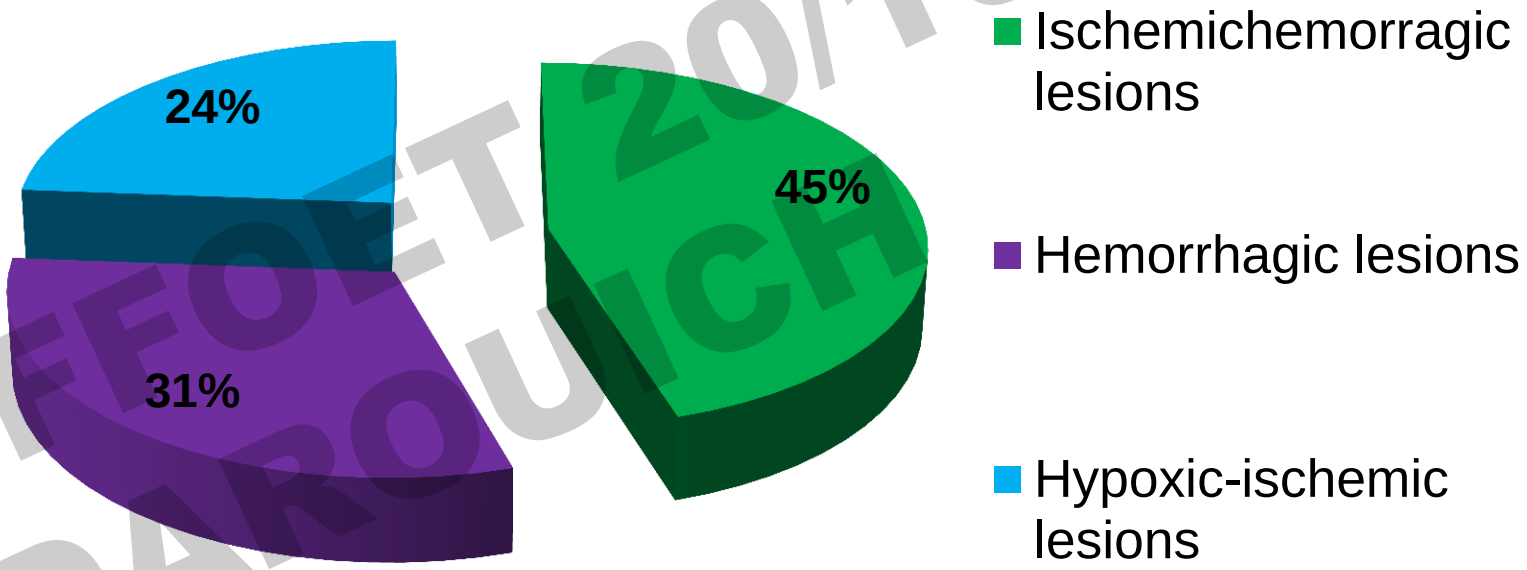


- AAS with abnormal patterning of the mesencephalon roof (tectum) and/or of the vermis
- Isolated AAS
- SAS with hypoplasia/agenesis of the medullary pyramids
- SAS without pyramids hypoplasia/agenesis

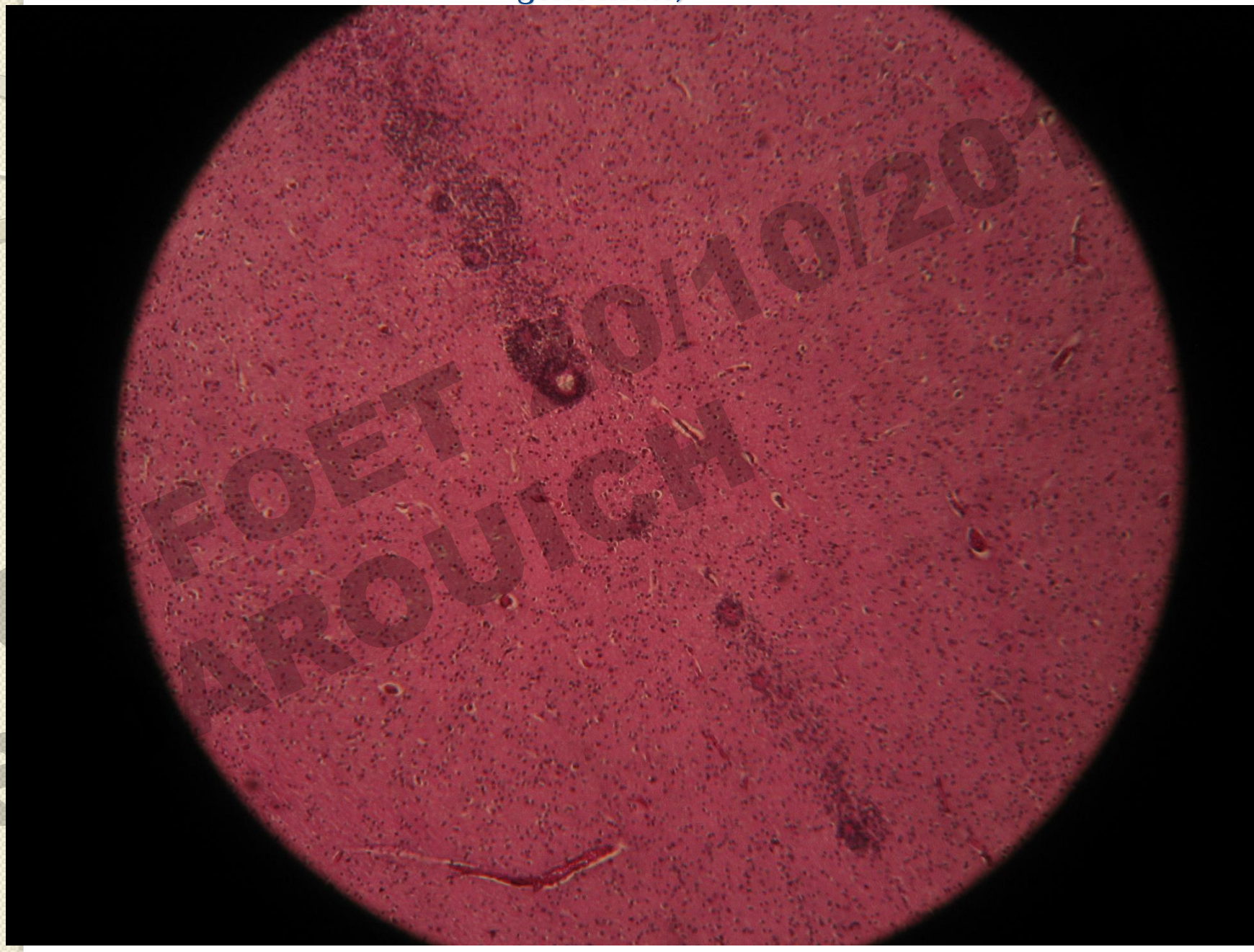
GROUP II: CEREBRAL CYTOARCHITECTONIC DISORDERS



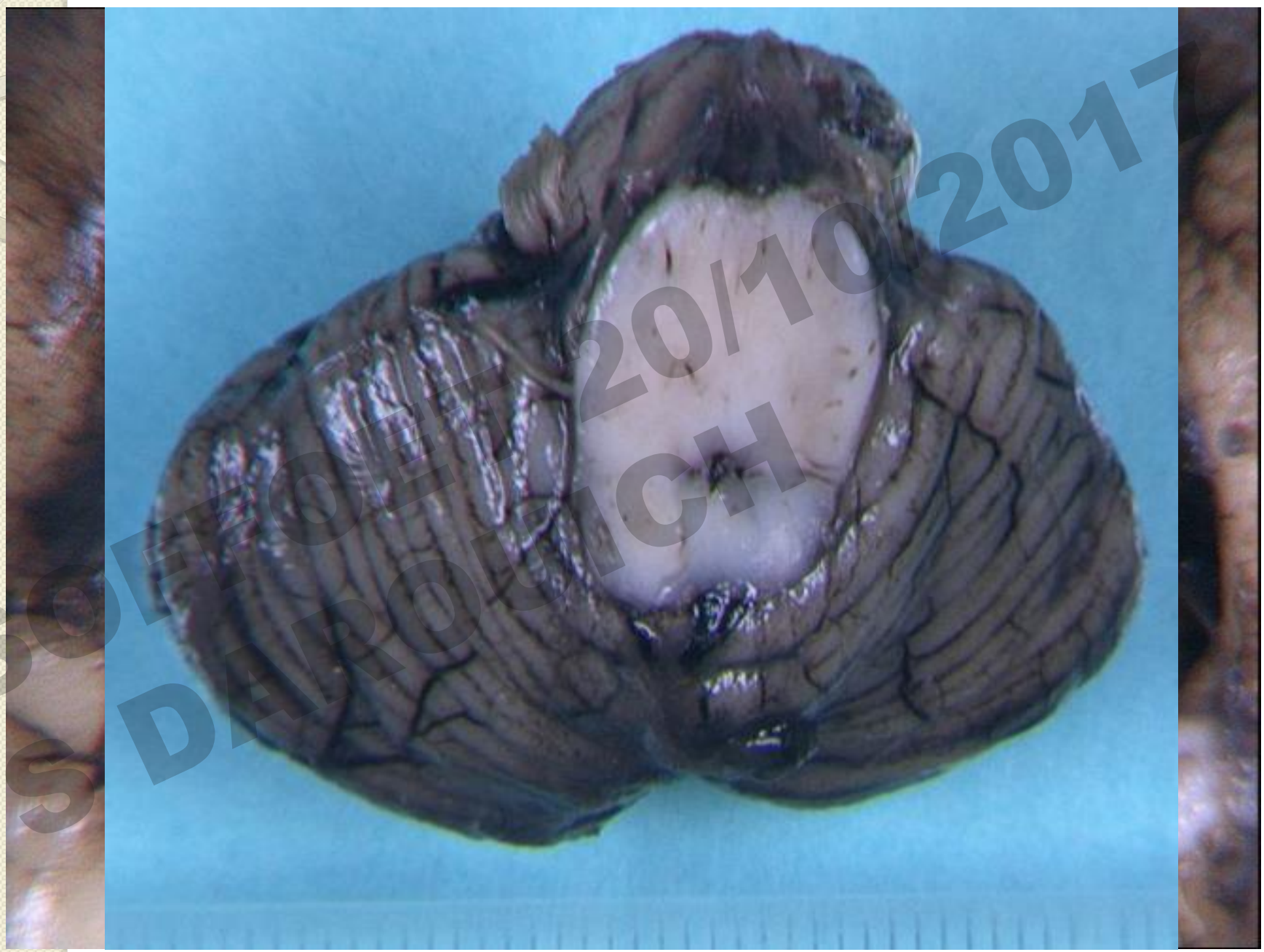
GROUP III: HEMORRHAGIC AND PERFUSION FAILURE



Atrésie de l'AS sans troubles de polarité dorso-ventrale (récurrence, pas de gène muté)



Sténose de l'AS associée à une hypoplasie des pyramides (*L1CAM* non muté)



Sténose de l'AS sans agénésie des pyramides (15q)

Etiology of fetal cerebral ventricular dilatation

	Group I	Group II	Group III	Group IV	Total
Total	54 (42%)	16 (12%)	42 (32%)	18 (14%)	130 (100%)
Chromosomal abnormalities	Dup 4q32.1q35.2 del 6q26q27 (case 27) Trip 15q11.2q13.1 dup15q13.3 (case 48)			Trisomy 21 (case 10) Del 17q21.31 involving *KANSL1* (case 5)	4 (3%)
Genetic mutation	Bicker-Adams syndrome (*L1CAM*; cases 37, 39) Pyruvate deshydrogenase deficiency (*PDHA1*; cases 40, 41) Chudley-McCullough syndrome (*GPSM2*; case 26)	Walker-Warburg syndrome *(POMT1, POMT2, POMGnT1, ISPD, B3GALNT2)* (cases 1-6) Tubilinopathy (*TUBB3*; case 8) Hypochondrodysplasia (*FGFR3*; case 12)	Porencephaly (*COL4A2*; case 26)	Type II osteogenesis imperfecta (*COL1A2*; cases 16, 17)	16 (12.3%)
Exogenous causes	Type 2 diabetes (case 33) Retinoid intoxication (case 30)		Gestational diabetes (case 9) Fetomaternal infection (case 18) Fetomaternal alloimmunization to platelet-specific antigen HPA-1α (case 22) Use of antiepileptic drug, sodium valproate (case 29)	Type 2 diabetes (case 11)	7 (5.4%)
Total	9/54 (17%)	8/16 (50%)	5/42 (12%)	5/18 (28%)	27/130 (20.7%)

Conclusions

Conclusion (1) Isolated atresia of the AS/V3 *MPDZ* mutation phenotype

Saugier-Veber *et al. Acta Neuropathologica Communications* (2017) 5:36
DOI 10.1186/s40478-017-0438-4

Acta Neuropathologica Communications

RESEARCH Open Access

Hydrocephalus due to multiple ependymal malformations is caused by mutations in the *MPDZ* gene

Pascale Saugier-Veber[1], Florent Marguet[2], François Lecoquierre[1], Homa Adle-Biassette[3], Fabien Guimiot[4], Sara Cipriani[5], Sophie Patrier[6], Marie Brasseur-Daudruy[7], Alice Goldenberg[8], Valérie Layet[9], Yline Capri[10], Marion Gérard[11], Thierry Frébourg[1] and Annie Laquerrière[2,12*]

Abstract

Congenital hydrocephalus is considered as either acquired due to haemorrhage, infection or neoplasia or as of developmental nature and is divided into two subgroups, communicating and obstructive. Congenital hydrocephalus is either syndromic or non-syndromic, and in the latter no cause is found in more than half of the patients. In patients with isolated hydrocephalus, *L1CAM* mutations represent the most common aetiology. More recently, a founder mutation has also been reported in the *MPDZ* gene in foetuses presenting massive hydrocephalus, but the neuropathology remains unknown. We describe here three novel homozygous null mutations in the *MPDZ* gene in foetuses whose post-mortem examination has revealed a homogeneous phenotype characterized by multiple ependymal malformations along the aqueduct of Sylvius, the third and fourth ventricles as well as the central canal of the medulla, consisting in multifocal rosettes with immature cell accumulation in the vicinity of ependymal lining early detached from the ventricular zone. MPDZ also named MUPP1 is an essential component of tight junctions which are expressed from early brain development in the choroid plexuses and ependyma. Alterations in the formation of tight junctions within the ependyma very likely account for the lesions observed and highlight for the first time that primary multifocal ependymal malformations of the ventricular system is genetically determined in humans. Therefore, *MPDZ* sequencing should be performed when neuropathological examination reveals multifocal ependymal rosette formation within the aqueduct of Sylvius, of the third and fourth ventricles and of the central canal of the medulla.

Keywords: *MPDZ* pathogenic variants, Foetal hydrocephalus, Neuropathology, Multifocal malformation of the ependyma, Autosomal recessive inheritance

Conclusion (2)

SAS without pyramids hypoplasia/agenesis

- Atypia of the sub-commissural organ : abnormal development of the SCO results in RF absence and may be associated with SAS as demonstrated in murine models of congenital CVD
- Possible role of this small glandular structure in the aqueductal morphogenesis

  (**Rodrıguez et al., 1998**)

Conclusion (3)
PERFUSION FAILURE

- COL4A1 and COL4A2 screening
- Correlation between ischemic villous changes and severity of cerebral lesions due to ischemic and/or hemorrhagic mechanisms

Thank you for your attention