

State of the Art

Alveolar Capillary Dysplasia

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Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV) is a rare, fatal developmental lung disorder of neonates and infants. This review aims to address recent findings in the etiology and genetics of ACD/MPV and to raise awareness of this poorly known disease, which may also present as milder, unclassified forms. Successively discussed are what is known about the epidemiology, pathogenesis, pathophysiology, diagnostic indicators and approaches, genetic testing, treatment, and cases of delayed onset. The review concludes with suggestions for future directions to answer the many unknowns about this disorder.

Keywords: interstitial lung disease; persistent pulmonary hypertension of the newborn; alveolar air–blood barrier; *FOXF1* transcription factor gene; comparative microarray analysis

The interstitial lung diseases of childhood, characterized by defective gas exchange, restrictive lung physiology, and diffuse involvement on lung imaging, include a heterogeneous group of conditions involving disordered development of the alveoli and distal airspaces (1, 2). Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV), the most common of these disorders, produces respiratory failure early in life and carries a mortality rate that approaches 100% (3). ACD/MPV is distinguished by immature lobular development and reduced capillary density, both of which indicate premature growth arrest. Distinct histological features allow for identification by a pathologist with a high index of suspicion and experience in diagnosing rare pediatric lung disorders.

Until recently, the primary clinical focus has been on early recognition and accurate diagnosis of ACD/MPV to avoid invasive and futile interventions for patients and their families. However, advances in our understanding of the genetics, pathology, and clinical features of the disease have begun to shed light on both the disease burden (revealing a potentially higher prevalence than originally thought) and underlying physiologic mechanisms. Furthermore, reports of infants presenting with fulminant symptoms of ACD/MPV well beyond the neonatal period, even as late as 7 months of age, have begun to emerge, challenging the established phenotype and offering the possibility that long-term survivors with milder forms of the disease may exist (4). DNA sequencing and comparative genomic hybridization have led to the identification of *FOXF1*

as one of the genes responsible for ACD/MPV and allowed for limited noninvasive diagnostic testing in some infants (5, 6).

As is true for most rare diseases, progress in understanding ACD/MPV depends on the identification of new cases and increasing awareness among health-care providers. Insights into the physiologic mechanisms underlying the development of ACD/MPV also may illuminate aspects of normal lung development that thus far have remained elusive. This review is presented with these considerations in mind.

HISTORICAL PERSPECTIVE

MacMahon made the first mention of “congenital alveolar dysplasia of the lungs” in 1947, when he described a condition “involving both lungs uniformly or only a portion of a single lobe” associated with abnormalities in other organs (7).

The seminal case reported by Janney and colleagues in 1981 (8) described a term neonate who developed severe respiratory distress 12 hours after birth and a clinical course consistent with persistent fetal circulation. Despite the best treatment available at the time, the infant developed severe bradycardia and hypotension and died at 40 hours of life. *Post mortem* examination of the lungs showed “failure of formation and ingrowth of alveolar capillaries”, abnormal air–blood barriers, and anomalous veins in the bronchovascular bundles. Janney and her team designated this entity of persistent fetal circulation with abnormalities of pulmonary vascular development “congenital alveolar capillary dysplasia.”

Since these early descriptions, more than 100 cases of ACD/MPV have been reported worldwide. Most of them have been sporadic, *de novo* events, but approximately 10% involved siblings, suggesting a heritable form of the disease (9–11). For several reasons, these case reports almost certainly underestimate the true prevalence of ACD/MPV. First, the definitive diagnosis of ACD/MPV currently depends on histological examination of lung tissue on autopsy or *ante mortem* lung biopsy, and neither of these diagnostic modalities is universally pursued in the setting of a critically ill or dying newborn (12). Second, many infants born with ACD/MPV have associated malformations in other organ systems that may allow the lung pathology to go undetected. Third, the diagnosis may be missed by pathologists unfamiliar with the disorder (13–16). Last, evidence is mounting to suggest that a less severe phenotype compatible with prolonged survival might exist, although definitive diagnostic criteria for this group are yet to be established (17–19).

EPIDEMIOLOGY

The incidence or prevalence of ACD/MPV is not yet known, but there are clearly more cases than those that have been reported formally in the literature. Furthermore, it seems likely that some cases originally classified as idiopathic persistent pulmonary hypertension of the newborn (PPHN) may actually

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have been ACD/MPV (14, 20). A slight male predominance (60%) has appeared in reported cases (21, 22). No geographic pattern is apparent; cases have been distributed worldwide.

More than 90% of affected infants are born at term (17, 21), and in greater than 60% of cases, onset of cyanosis and respiratory failure occurs within 48 hours of birth (9, 23). In a recent review of 21 cases of ACD/MPV from England, Melly and colleagues (24) proposed that the severity of disruption in capillary density and lack of contact with the alveolar epithelium may be two major factors that determine clinical course and prognosis, and they ascribed the potential for survival beyond the neonatal period in a minority of patients to higher capillary density and apposition. The prevalence of this milder, potentially survivable phenotype is not known.

The number of infants with ACD/MPV treated with extracorporeal life support is unknown, but several case series cite infants with unexplained PPHN who fail to improve with full cardiopulmonary support (15, 25). Twenty-two percent of neonates referred for PPHN do not survive, according to 2010 Extracorporeal Life Support Organization registry data (26). Given the decrease in extracorporeal membrane oxygenation (ECMO) referrals for PPHN (27, 28) and the generally favorable outcomes, this group of nonsurvivors may include infants with ACD/MPV.

PATHOGENESIS

The pathogenesis of both ACD/MPV and its associated pulmonary hypertension remain to be fully explained. Cullinane and colleagues (13) were the first to suggest that the primary pulmonary vascular anomaly is a failure of fetal lung vascularization in response to an unknown teratogen. With the number of pulmonary capillaries drastically reduced, blood entering an individual lung unit can only drain via anomalous (“misaligned”) veins. The obstruction that is created leads to the occlusive changes observed in the pulmonary arterial circulation. Sirkin and colleagues (29) shared the view that an early antenatal insult

leads to a deficient pulmonary capillary bed and a decreased bronchial generation count, and suggested a genetic defect could explain both the extrapulmonary findings and ACD/MPV occurrence in families. Others have proposed that the muscular thickening in the small pulmonary arteries may be the primary lesion, resulting from pulmonary vasoconstriction, with consequent failure of normal alveolar capillary development (30). However, this latter theory does not adequately explain the vascular changes observed *in utero*, because gas exchange does not involve the alveolar capillary interface before birth. Further identification of the genetic mechanisms involved in the pathogenesis of ACD/MPV will likely clarify the underlying defect in pulmonary vascular development that results in irreversible hypoxemia and pulmonary hypertension and explain the characteristic patterns of functional response to therapy.

PATHOPHYSIOLOGY AND DIAGNOSIS

Physical and Laboratory Findings

Key diagnostic criteria are summarized in Tables 1 and 2. Infants with ACD/MPV usually present with minimal or no parenchymal lung disease. Profound hypoxemia, with partial pressures of oxygen in arterial blood less than 30 mm Hg, and severe metabolic acidosis consistent with pulmonary hypertensive crisis and right ventricular failure are nearly always present. However, to date, no routine laboratory tests can distinguish ACD/MPV from other causes of neonatal pulmonary hypertension. Blood gases may support the diagnosis, but threshold values that are pathognomonic for ACD/MPV have not been identified. ACD/MPV should always be considered in infants with idiopathic PPHN whose symptoms recur after successful weaning from ECMO (31, 32).

Extrapulmonary findings are present in 50 to 80% of cases (10, 14, 21, 25, 30, 33, 34). Therefore, an infant with unexplained respiratory failure and structural abnormalities of the genitourinary, gastrointestinal, or cardiovascular systems should be

TABLE 1. KEYS TO DIAGNOSIS

| | |
|---------------------------|---|
| Perinatal | Prenatal risk factors: none identified Gestation: full term (> 90%) Apgar scores: not predictive (often 8 or 9 at 1 and 5 min) Symptom onset: 24–48 h after birth (> 60%) or weeks to months (delayed presentation) |
| Presentation (variable) | Classic neonatal presentation PPHN: tachypnea, cyanosis, respiratory distress Acute hypoxemic respiratory failure Idiopathic pulmonary hypertension Delayed presentation Asymptomatic or mild tachypnea at birth; ± transient oxygen requirement; may be evaluated for sepsis |
| Course | Early (at symptom onset) Transient response to pulmonary vasodilators, mechanical ventilation, extracorporeal life support Later (hours to weeks) Unremitting pulmonary hypertension Second course of ECMO not curative Uniformly fatal without lung transplantation |
| Associated anomalies | Important diagnostic clue when present with unexplained PPHN Most commonly: gastrointestinal, genitourinary, cardiac systems (detailed in Table 2) |
| Imaging (nondiagnostic) | Chest radiograph: normal, hazy, or diffuse ground-glass pattern; pneumothoraces may be present early or develop late Echocardiogram: pulmonary hypertension (right ventricular hypertrophy, bowing of IVS into LV, tricuspid regurgitation) PFO or PDA Cardiac catheterization: often no structural heart lesion |
| Laboratory tests | Normal, delayed, or absent capillary blush phase Not pathognomonic |
| Pathology (gold standard) | Characteristic histology (detailed in Table 3) |
| Genetics | Approximately 10% of cases are familial Microdeletions, point mutations in or upstream to the <i>FOXF1</i> gene on chromosome 16q24.1 (~ 40%) |

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; IVS = intraventricular septum; LV = left ventricle; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PPHN = persistent pulmonary hypertension of the newborn.

TABLE 2. EXTRAPULMONARY ANOMALIES ASSOCIATED WITH ALVEOLAR CAPILLARY DYSPLASIA WITH MISALIGNMENT OF THE PULMONARY VEINS

| System | Examples (References) |
|------------------|--|
| Gastrointestinal | Intestinal malrotation (10, 14–16, 30, 34, 46, 63) Esophageal atresia (14) Tracheoesophageal fistula (14, 15) Anal atresia (14, 51) Absent gallbladder (10, 14, 29, 34) Postpyloric ectasy of the small intestine (34, 64) Omphalocele (23) Duodenal stenosis (14, 21, 34, 63) Meckel diverticulum (34, 59) Arteriovenous malformation of the liver (cavernous hemangioma) (10, 20) Volvulus of the small bowel (34, 63) Total absence or decreased number of ganglionic cells of the colon (10, 14, 15, 39, 63) Redundant colon (14, 15, 34, 63) Imperforate anus (10, 14, 20, 34) Annular pancreas (14, 30, 34) Asplenia (14, 22, 34, 43) |
| Urogenital | Bilateral ureteropelvic junction obstruction with hydronephrosis (9, 10, 34) Bilateral hydronephrosis, posterior urethral valves (10, 15, 34, 63) Bladder hypertrophy (10) Hydroureter (10) Stenosis of the distal ureters with hydronephrosis (34, 37, 65) Bicornuate uterus (8, 34, 63, 66) Cryptorchidism (9, 15, 34) |
| Cardiovascular | Hypoplastic left heart syndrome, left outflow tract stenosis (10, 34, 40, 44) Bicuspid aortic valve (21, 40) Patent ductus arteriosus (43, 44) Atrial septal defect (10, 43, 44) Atrioventricular septal defect, quadricuspid pulmonary valve (40) Pulmonary valvular and subvalvular stenosis (43) Malformed mitral and tricuspid valves (10, 59) Retrosophageal subclavian artery (34, 63) Continuation of the left superior vena cava with the coronary sinus (18, 34) Absent right umbilical artery (34) Cor triatriatum, nonobstructive (10, 34, 43, 46) |

evaluated for ACD/MPV (10, 33). Additionally, disruption of right–left asymmetry of the intrathoracic and/or intraabdominal organs has been reported in more than 25% of cases (10). ACD/MPV has occurred in infants with Down syndrome; the existence of one does not preclude the other (35).

Imaging Studies

The chest radiograph may show diffuse haziness or subtle ground-glass opacities but is often interpreted as normal. Pneumothoraces have been reported frequently in patients with fulminant disease, but it is not entirely clear whether this feature is related to abnormalities in lung architecture or surfactant function, a consequence of aggressive ventilator treatment to reverse hypoxemia, or is some combination of the two. To date, there are no reports of computed tomography or magnetic resonance lung imaging in infants with documented ACD/MPV.

An echocardiogram is performed to exclude a cardiac cause for pulmonary hypertension. Although the images will typically demonstrate suprasystemic right ventricular pressures and right-to-left shunting through a patent ductus arteriosus or a patent foramen ovale, these findings are not specific for ACD/MPV.

The presence of delayed or absent capillary blush phase on pulmonary angiography has been reported in a small series of

patients with ACD/MPV who underwent cardiac catheterization for evaluation of pulmonary hypertension (36). At present, this finding is only supportive and cannot be used as a substitute for histopathologic diagnosis.

Confirmatory Diagnosis

Currently, definitive diagnosis of ACD/MPV is based on histological examination of lung tissue by a pediatric pathologist with prior experience in diagnosing ACD/MPV. The characteristic histological features of ACD/MPV are listed in Table 3 and can be seen in Figure 1.

Genetic Testing

In a recent published report (5), mutations or deletions in the *FOXF1* transcription factor gene or deletions upstream to *FOXF1* were identified in 40% of cases. Blood testing to screen for these defects is now available, but a negative result does not preclude the diagnosis, and histological examination of lung tissue remains the gold standard. Currently, the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston is the only center known to be screening prenatally and postnatally for mutations and deletions. *FOXF1* mutation analysis is a first step toward providing prenatal diagnosis for families at high risk.

Lung Biopsy

Thus far, approximately 90% of reported cases of ACD/MPV have been diagnosed on autopsy, and 10% of diagnoses have been made from lung tissue obtained during *ante mortem* lung biopsy. Although an infant may appear too unstable to tolerate an operative procedure, a positive biopsy provides important prognostic information and helps to dictate the care plan (37). Both open and thoracoscopic biopsy approaches have been used successfully (38).

The diagnostic yield from an operative lung biopsy is in large part dependent on surgical technique and proper handling of the tissue specimens. The Children's Interstitial Lung Disease (chILD) Pathology Cooperative Group, under the leadership of Dr. Claire Langston, developed a protocol for the handling of tissue obtained from operative lung biopsy (39). These comprehensive guidelines, which include recommendations for biopsy sites, sampling techniques, specimen size, tissue staining, and sample processing, are intended to standardize the approach to pathologic diagnosis to achieve optimal results.

It is likely that cases of ACD/MPV have been missed due to parents refusing autopsy or to reticence on the part of some health-care providers to advocate strongly for *post mortem* studies. As awareness of ACD/MPV among caretakers increases, it is anticipated that more infants will undergo *ante mortem* lung biopsy, yielding additional cases for study.

Differential Diagnosis

The following diagnoses should be excluded when evaluating an infant for ACD/MPV (22, 40–42):

1. Idiopathic PPHN, which is generally distinguished from ACD/MPV by its reversibility, most often resolving completely with pulmonary vasodilators, respiratory support, and/or ECMO;
2. Sepsis, pneumonia, and other infectious etiologies;
3. Primary respiratory disorders, including abnormalities of surfactant production (e.g., surfactant protein B deficiency, transporter abnormalities) or function (including hyaline membrane disease), pulmonary hypoplasia, con-

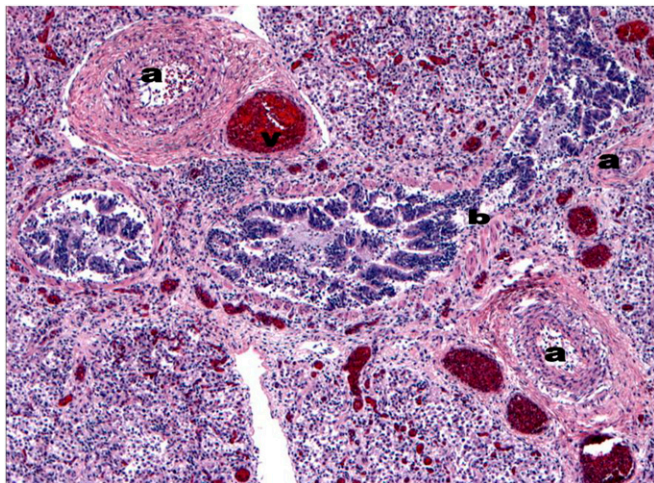


Figure 1. Hematoxylin and eosin staining of an autopsy specimen from an infant who presented at 5 weeks demonstrates the characteristic histologic features of ACD/MPV: small pulmonary arteries with medial hyperplasia (a), congested pulmonary veins malpositioned within the same adventitial sheath (v), and a dilated bronchiole (b). Additional findings, (i.e., neutrophilic infiltrate and hemorrhage) are consequences of the hypoxemic respiratory failure and aggressive ventilatory support. (Courtesy of the Weill Cornell Medical College Department of Pathology and Laboratory Medicine.)

genital diaphragmatic hernia, and other rare diffuse interstitial lung disorders (e.g., acinar dysplasia, congenital alveolar dysplasia) (24);

4. Congenital cardiopulmonary diseases associated with severe cyanosis and/or pulmonary hypertension, most notably pulmonary venous stenosis and total anomalous pulmonary venous return. However, it should be remembered that cardiac lesions have been reported in up to 25% of children with ACD/MPV (10, 16, 34, 40, 43–45);
5. Neurologic disorders, including perinatal asphyxia and congenital neuromuscular disorders.

GENETICS: PAST AND FUTURE APPROACHES

The genetic etiology of ACD/MPV has remained elusive for decades (46). Pedigree analyses of ACD/MPV patients' families have suggested both autosomal dominant and recessive patterns of inheritance (10), thus implicating at least two causative genes.

TABLE 3. CONFIRMATORY DIAGNOSIS

| Histopathologic Features |
|---|
| Immature lobular development |
| Decreased number of pulmonary capillaries located away from the alveolar epithelium |
| Thickened alveolar septae |
| Medial hypertrophy of small pulmonary arteries and muscularization of distal arterioles |
| Malposition of pulmonary vein branches adjacent to pulmonary arteries (same adventitial sheath) |
| Lymphangiectasis (30%) |

Data from References 10, 13, 30.

Early (Abandoned) Candidate Genes: *STRA6*, *BMP2*, and *AIMP1*

Previously investigated candidate genes include the *STRA6* (stimulated by retinoic acid 6) gene, which has been implicated in patients with ACD features and other malformations such as anophthalmia (47), the *BMP2* (bone morphogenetic protein 2) gene, and the *AIMP1* (previously known as *EMAP II*, endothelial monocyte-activating polypeptide II) gene. None of these genes was found to have been mutated in a group of patients with ACD/MPV; furthermore, the lung changes reported in those with *STRA6* mutations did not include misalignment of pulmonary veins.

Genomic Deletions at 16q24.1

In 2009, Stankiewicz and colleagues (5) described the identification of different-sized overlapping submicroscopic genomic deletions in chromosomal region 16q24.1q24.2 in six unrelated patients with histopathologically verified sporadic ACD/MPV and other congenital malformations. These microdeletions were detected using array comparative genomic hybridization and ranged in size from approximately 100 kb to approximately 3.5 Mb. No deletions in this genomic region are found in different databases of genomic variants, indicating that these changes are pathogenic.

A Candidate Gene

The smallest region of overlap of the identified deletions at chromosomal region 16q24.1 contained the *FOX* transcription factor gene cluster, including *FOXF1*, *FOXC2*, and *FOXL1*. *FOXF1* (Forkhead Box-F1, previously known as *HFH-8* or *FREAC-1*) proved to be a very good candidate gene for ACD/MPV given its expression pattern (i.e., expressed in mesodermal endothelial and smooth muscle cells in the fetal and adult lung) and the abnormalities described in a previously reported murine model.

Animal Model of ACD

The murine model of *FOXF1* deficiency was developed in Chicago in 2001 in the laboratory of Robert Costa, Ph.D. (48). Mouse embryos with homozygous (i.e., both copies) deficiency of *Foxf1* all died by 8.5 days post coitum due to pulmonary vascular abnormalities. Interestingly, of the heterozygous mice (i.e., those with only one copy of the gene deficient), half lived without symptoms as normal mice, whereas the remainder had abnormal alveolar development and died with pulmonary hemorrhage in the setting of severe defects in alveolarization and vasculogenesis (49, 50). Their pulmonary histopathologic changes included some but not all of those seen in human infants with ACD/MPV, and because of this incomplete recapitulation, the connection to ACD/MPV was not made at the time.

To explain these unusual phenotypic findings, Kalinichenko and colleagues measured the levels of the *Foxf1* protein in heterozygous *Foxf1*-deficient mice and observed that normal mice restored the decreased level of *Foxf1* protein at the end of gestation, whereas affected mice did not. This was interpreted as “compensation” for the alveolarization defect (48).

FOXF1

To determine whether *FOXF1* is pathogenic for ACD/MPV in humans, Stankiewicz and colleagues (5) sequenced *FOXF1* in a cohort of 18 patients with ACD/MPV and other malformations collected at Baylor College of Medicine in Houston. This research team identified four different *de novo* heterozygous inactivating (frameshift, nonsense) point mutations in the

coding sequence of *FOXF1* in this group of unrelated patients with sporadic ACD/MPV, thus proving that *FOXF1* is a pathogenic gene. In the remaining mutation-negative ACD/MPV cases, a 16q24 region-specific high-resolution oligonucleotide microarray analysis revealed three *de novo* deletions in 16q24.1 (5), further confirming that *FOXF1* is a dosage-sensitive (haploinsufficient) gene, responsible for approximately 40% of ACD/MPV cases, representing a new genomic disorder. The presence of two upstream deletion copy number variants leaving *FOXF1* intact, as well as the intriguing fact that all the analyzed deletions were of maternal inheritance, indicated that other molecular mechanisms, such as position effects and genomic imprinting, may operate at this FOX gene cluster locus.

In contrast to the association of point mutations in *FOXF1* with bowel malrotation, microdeletions of *FOXF1* were found in patients with ACD/MPV who also manifested hypoplastic left heart syndrome and gastrointestinal atresias, likely due to haploinsufficiency for the neighboring *FOXC2* and *FOXL1* genes. These differences reveal the phenotypic consequences of gene alterations in *cis*.

The additional anomalies, cardiac malformations, esophageal and anal atresia, renal and vertebral/axial malformations, which are variably present in up to 80% of patients with ACD/MPV with deficiency of *FOXF1*, are also common findings in patients with VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal, and limb malformations) association. Thus, the identification of *FOXF1* may contribute to unraveling the molecular bases of the VACTERL association.

Search for the Other ACD/MPV Gene(s)

Studies in humans and mice have revealed that the *FOXF1* protein is involved in sonic hedgehog signaling, implying that other genes from this well-known and important pathway may be involved in the etiology of ACD/MPV.

Currently, the most promising approaches for novel gene identification are next-generation sequencing technologies that have been successfully applied for both whole-genome and whole-exome sequencing. These methodologies have already enabled identification of several new genes (51–53). Although still relatively expensive, these technologies will soon be used in sequencing some ACD/MPV samples from pedigrees that suggested both autosomal dominant and recessive inheritance. For families showing autosomal recessive pattern inheritance, the addition of single-nucleotide polymorphism microarrays may be of help in narrowing the critical region associated with ACD/MPV.

Identification of additional ACD/MPV genes would be broadly informative to the general biology and pathophysiology of human lung development. In particular, these data may contribute to a better understanding of the etiology of pulmonary hypertension, a characteristic feature of ACD/MPV and a common pulmonary disorder.

TREATMENT

The clinical approach to infants with ACD/MPV is no different than that for other neonates presenting with PPHN. However, the response to therapy is often minimal and/or not sustained, which may serve as an initial diagnostic clue.

Because the hypoxemia is so severe and unrelenting, many practitioners will attempt lung recruitment strategies, such as high-frequency ventilation or surfactant. However, infants with ACD/MPV usually present with minimal parenchymal lung disease. Lung recruitment strategies may induce respiratory alkalosis and a transient improvement in oxygenation, but may also contribute to rapid deterioration due to lung overdistension and associated compromise of right atrial filling. Recent case

series have reported high rates of unilateral or bilateral pneumothorax, which could be another consequence of excessive airway pressures (20, 54).

Most infants with ACD/MPV will develop progressive hypotension due to right ventricular failure and/or refractory hypoxemia. Because the hypoxemia and pulmonary hypertension cannot be effectively reversed, cardiotoxic agents have only a minimal or transient effect in infants with ACD/MPV.

Although transient responses to pulmonary vasodilator therapy can be observed in infants with ACD/MPV, no infant has been reported to have a sustained response to any available pulmonary vasodilator. In a study of five infants with documented ACD/MPV, all responded to inhaled nitric oxide with improved oxygenation (>200 mm Hg) and reduced pulmonary artery pressures, but deterioration and death followed within hours (25). Other reports have demonstrated a similar pattern of response to inhaled or intravenous prostacyclin (55, 56), suggesting that the pattern of initial improvement followed by deterioration may be specific to the anomalous vasculature of ACD/MPV. To date, there are no reports of sildenafil use in infants with ACD/MPV.

ECMO is used at some point in the clinical course in most case series of ACD/MPV, and a report from the U.K. ECMO experience found that ACD/MPV was diagnosed in 14% of babies who died after ECMO support. This was almost certainly an underestimate, as ACD/MPV was documented in 33% of babies who had full autopsy examinations (12). At least one additional report showed that ACD/MPV was found in the majority of infants with idiopathic PPHN who did not respond to ECMO (six of seven infants) (20). The registry maintained by the Extracorporeal Life Support Organization indicates that more than 20% of infants with idiopathic PPHN do not respond to ECMO support, which should prompt investigation for ACD/MPV (20, 57).

Because none of the supportive therapies described above has changed the expected mortality due to ACD/MPV, lung transplantation is currently the only option that might prolong survival. Although successful lung transplantation in infants with ACD/MPV has not been reported, achieving early diagnosis by lung biopsy is an essential first step, followed by strategies that sufficiently prolong survival. A recent report demonstrated survival of an infant for more than 3 months after presentation in the neonatal period (58), indicating that lung transplantation may provide effective treatment for carefully selected affected infants.

LATE PRESENTERS AND LONG-TERM SURVIVORS

Reports of infants presenting with clinical features of ACD/MPV beyond the neonatal period have begun to emerge. Thus far, four reports of infants presenting with fulminant disease at 5 weeks, 7 weeks, 12 weeks, and 7 months have been published (4, 18, 19, 59). Although two of them presented with symptoms serious enough to warrant brief periods of respiratory observation in a neonatal intensive care unit before discharge (4, 59), the remaining two appeared asymptomatic and were discharged home as well babies (18, 19). With such limited information, it is difficult to estimate the number of patients with delayed presentation of ACD/MPV, but it is certainly greater than the four mentioned above. Until more specific diagnostic tools become available, similarities in lung pathology and clinical findings should increase diagnosis using the same approach to lung tissue sampling in late presenters as for those who present early.

The pathophysiology underlying the development of ACD/MPV has yet to be fully characterized, and mechanisms that might explain delayed presentation are even less clear. How

infants with structural defects at the level of the air–blood barrier can remain virtually asymptomatic for weeks or months is one of the urgent questions now under investigation. The findings of Melly and colleagues (24) suggest that variations in disease severity and timing of presentation correspond to alterations in capillary density and contact with the alveolar epithelium. Better lobular development and patchy involvement have also been cited to explain the delay in onset of symptoms (9, 30, 60), but this remains controversial. In fact, thus far, the histological appearance of lung tissue taken from early and late presenters has been strikingly similar (4). As such, mechanistic explanations for delayed presentation of ACD/MPV will require the identification of triggers for the acute deterioration that signals the onset of fulminant disease. One of the most plausible explanations suggests that the onset of symptoms, whether early or delayed, results from vasoconstriction of a hypertrophied arterial bed (30), which then triggers a pulmonary hypertensive crisis. Interestingly, viral upper respiratory infections, known to trigger pulmonary hypertension in those at risk, were reported in two of the late presenters. Regardless, the remarkable overlap in clinical course and outcome of infants with advanced disease, whether the onset is early or delayed, requires further investigation.

There appears to be no survival advantage in presenting late. Once symptoms develop, the infant with delayed presentation of ACD/MPV experiences the same downward spiral that results in death.

A better understanding of the genetic and physiologic mechanisms that govern the ACD/MPV phenotype and timing of presentation may lead to expanding the current case definition to include long-term survivors. Of note, a recent case report in the *British Journal of Radiology* (61) described a 21-year-old woman with newly diagnosed pulmonary hypertension and “misplaced pulmonary arteries” located in the interlobular septae (in addition to ones that were located normally in the bronchovascular bundles). Although disputed, the authors claim that the histological findings are similar to those described in newborns with PPHN and may represent a forme fruste of the vascular anomaly seen in ACD/MPV. If replicated, their findings would lend support to the hypothesis that milder, survivable forms of the disorder exist.

FUTURE DIRECTIONS

Advances in ACD/MPV genetics research, combined with support from federal health-related research agencies, such as the Centers for Disease Control and Prevention and the National Institutes of Health, are providing an impetus for ongoing investigation into several aspects of this rare disease. Steadfast commitment by researchers and rare disease coalitions, academic research networks such as the Children’s Interstitial Lung Disease Research Network (chILDRN), parent advocacy groups, and others, along with encouraging developments in the areas of genetic technology (i.e., the availability of oligonucleotide comparative genomic hybridization and exome sequencing) and electronic database development (with the impending launch of a state-of-the-art interactive international electronic database for rare lung diseases in children) should accelerate the rate at which further progress will be made.

With this foundation, future activities should place emphasis on the following goals:

1. To identify additional genes or genetic mechanisms operating at the *FOXF1* locus involved in the pathogenesis of ACD/MPV, which may elucidate complex phenotype–genotype relationships;
2. To define regulatory mechanisms that determine phenotype, disease severity, timing of presentation, natural history, and outcomes;
3. To refine existing animal models of ACD/MPV (49, 62) for the purposes of developing prenatal and postnatal diagnostic tests and exploring new approaches to treatment;
4. To increase awareness and disseminate information about ACD/MPV across a broad spectrum of health-care providers;
5. Through the above activities, to identify a greater number of cases that can generate reliable and valid data for the purposes of developing accurate diagnostic criteria and preferred treatment practices.

It is through the accomplishment of the above goals that ACD/MPV may transform from a uniformly lethal disorder into one that is treatable and/or preventable.

SUMMARY

ACD/MPV is a rare, lethal, neonatal developmental lung disorder that results in abnormal alveolar air–blood barriers for gas exchange, severe hypoxemia, and pulmonary hypertension. It may be distinguished from idiopathic PPHN by an incomplete response to interventions known to be effective in PPHN, the presence of associated anomalies of the gastrointestinal, genitourinary, and cardiovascular systems, and occasionally by onset beyond the early neonatal period. Histologic evaluation of lung tissue is the current gold standard for diagnosis and is most often performed at autopsy. Early *ante mortem* surgical lung biopsy can also provide the diagnosis, but the index of suspicion among health-care providers must be high. The *FOXF1* gene has been identified as being responsible for ACD/MPV in 40% of cases examined, and additional candidate genes and potential defects are being investigated. We recommend development of an expanded registry to improve our understanding of the ACD/MPV phenotype, pathophysiology, and genetics.

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