CEREBROPULMONARY DYSGENETIC SYNDROME

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Abstract

Ventilatory treatment of neonatal respiratory distress often results in bronchopulmonary dysplasia from congenital surfactant deficiency due to mutants of transporter protein ABCA3. Association of this condition with other severe disorders in premature newborns has not heretofore been reported. A neonatal autopsy included an *in vivo* whole blood sample for genetic testing. Autopsy revealed severe interstitial pulmonary fibrosis at age 8 days with heterozygotic mutation p.E292V of ABCA3 and severe dystrophic retardation of cerebral cortex and cerebellum. Subsequently, 1300 archival neonatal autopsies, 1983-2006, were reviewed for comparable concurrent findings and bronchopulmonary dysplasia or retarded cerebral dystrophy lacking the other principal feature of this syndrome. Archival review revealed four similar cases and eight less so, without gene analysis. Further review for bronchopulmonary dysplasia revealed 59 cases, 1983-2006. Several other examples of similar retarded migration of germinal matrix and underdevelopment of cortical mantle, without pulmonary lesions of this type, were identified. The determination of an ABCA3 mutation in one case of severe pulmonary fibrosis with significant dystrophy of the brain and the identification of four highly similar archival cases and eight others with partial pathological findings supports the designation of an independent disorder, here referred to as the *cerebropulmonary dysgenetic syndrome.*

Key Words

Bronchopulmonary dysplasia, respiratory distress syndrome, heterozygotic mutation, retarded cortical neuronal migration, ABCA3 mutation, surfactant deficiency, lung fibrosis, congenital fibrosis of thyroid, cerebral dystrophy, cerebropulmonary dysgenetic syndrome

The first description and pathogenetic study of bronchopulmonary dysplasia, a complication of the evolving treatment of neonatal respiratory distress of the day, was forty years ago by Northway, Rosan, and Porter (1967). Interstitial pulmonary hypercellularity and progressive fibrosis were the principal features of the lung lesion when first described by them whereas others, such as Robertson (1963, 1964) and Barter, et al. (1966) emphasized the findings in the terminal airspaces. Indeed, Barter, et al.(1966) noted hyaline membrane formation was rarely seen in infants only four days old, describing their observations as *late results*.

By contrast, Northway and associates continued after 1967 to call attention to and to make further observations on the interstitial component of longer term sequelae of pressure based ventilatory support and oxygen enrichment (Northway and Rosan, 1968; Northway and Rosan, 1969; Bonikos et al., 1976; Edwards et al., 1977; Northway, 1979; Northway, 1990; Northway et al., 1990; Northway, 1992; Howling et al., 2000). An early study of the long term radiographic findings dates from 1968. (Shepard et al., 1968). Improvements in neonatal treatment since then have engendered more detailed studies of the progressive lung lesions identified in infants four to ten months old (Erickson et al., 1987) and young adult survivors (Howling et al., 2000).

This more recent emphasis has overshadowed early work on the first phase of the lesion complex of hyaline membrane disease, including associated interstitial and air space hemorrhage, (Shanklin and Wolfson, 1967), and focal necrosis of terminal bronchiolar epithelium (Barter et al., 1966; Shanklin, 1971; de la Monte et al., 1986).

Evidence is now accumulating for a genetic factor in the ability of the pulmonary interstitium to respond to either the primary pathogenesis or as an adverse factor in lung healing over time, or both, specifically mutations of the gene for ATP-binding cassette transporter protein, ABCA3 (Matsumura et al., 2006; Somaschini et al., 2007; Guala et al., 2007).

This development offers an explanation for early severe onset of pulmonary fibrosis with a high failure rate in hyaline membrane disease and led, in the index case, to the discovery of another serious developmental defect, in the brain. This combination of lesions, perhaps with other associated findings, has implications challenging for diagnosis, both clinical and pathological, and neonatal intensive care, and for further research at molecular, cellular, and genetic levels.

Clinical history.

Prenatal course was normal for a 30 year old primigravida until the 34th week when labor began by premature rupture of membranes. Betamethasone and penicillin G were given before the spontaneous vaginal delivery, after a total labor of 18 hours. The neonatal Apgar scores were **8** at 1 minute, **9** at 5 minutes. A female infant weighed 1770 grams. Curosurf (1 dose) and face oxygen were provided. There was deterioration of cardioventilatory activity and she was placed on nasal CPAP, thence mechanical ventilation at 17.5 hours of life. Chest films showed hazy granular lungs with air bronchograms. Blood cultures were negative. The infant remained refractory and was transferred to

our NICU on the 4th day and placed on the oscillator. The ductus was patent with bidirectional flow by echocardiogram; there was a dilated left atrium and cardiomegaly.

Pressor support was by *dopamine* and *dobutamine* and *Indocin* to close the ductus (3 doses). Antibiotics were continued. The next four days were complicated by refractory respiratory failure, persistent hyaline membrane disease, marked hypercarbia, severe acidosis, hypotension, and secondary cardiac failure. The CRP rose >5.0 mg/dl; on the 7th day the final WBC was 6,000mm^3. On the 8th day, tension pneumothorax occurred which was treated by drainage tube. A patient management conference with family discussed the poor prognosis: the decision was made to withdraw active support, replaced by comfort care.

Placental and autopsy findings.

The placental:fetal weight ratio was 0.197, a median value for 34 weeks. There was generally normal development and maturation of the villi, dilation and hypertrophy of deeper vascular networks, and marginal trophoblastic hyperplasia and decidual redundancy consistent with zonal *placenta extrachorialis.* The autopsy proper revealed: (1) unresolved somatic prematurity, (2) far advanced active progressive pulmonary fibrosis with focal remnants of hyaline membrane formation, (3) superimposed acute bronchiolitis and pneumonia, (4) myeloid hyperplasia, marrow and myeloid metaplasia, hepatic portal triads, (5) terminal systemic leukemoid reaction, (6) advanced cortical depletion of thymus, (7) cerebrocerebellar dystrophy consisting of general retardation of cerebral glioneuroblast migration, retention of much of the paraventricular germinal matrix (with *in situ* maturation), stasis of proximal migratory germinal matrix, absence of protopyramidal neuronal differentiation in layer 5 of parietal (motor) cortex, neuronal

underpopulation and immaturity of cortical mantle; dyssynchrony of purkinje cell maturation, cerebellum, with retarded development and maturation of the outer folia, and focal arteriovenous malformations in the occipital cortical and cerebellar meninges, mesencephalon, and pons, (8) biventricular myocardial hypertrophy (35% above median value for body mass), (9) an endocrinopathy of uncertain type: retarded follicle formation, thyroid, with markedly enhanced trabecular fibrosis; eosinophile dominance, anterior pituitary; adrenal hypoplasia (combined weight, 2.8 g, median for birth weight, 4.8 ± 0.3 g); hypoplasia of provisional adrenal cortex; hyperplasia and early maturation, adrenal medulla, and one adrenal cortical nodule. Accessory findings included patent ductus arteriosus, small focal intrafolial cerebellar hemorrhages, minimal neuronal injury, extramedullary erythropoiesis of liver and spleen, focal myelopoiesis of central axial lymph nodes, isolated thrombosis of a renal arcuate artery, thrombosis/embolus in a marrow nutrient artery, status left post pneumothorax, and status intravascular line placements.

Specifically illustrated are the intense lung fibrosis (Figure 1), the remnants of germinal matrix and in situ maturation (Figure 2), the immature parietal cortex lacking pyramidal cells in layer 5 (Figure 3), and trabecular fibrosis of an immature, likely hypofunctional thyroid (Figure 4).

Genetic report.

From Ambry Genetics (Aliso Viejo, CA): heterozygotic mutation of ABCA3 full gene, known mutation p.E292V, the same mutation found in case #8 of Somaschini, et al. (2007), in 10 of 11 patients reported by Bullard, et al. (2005) but not by Matsumura, et al.(2006) or Shulenin, et al.(2004).

No novel or other reported variants were identified.

Archival investigation.

Twelve cases with lung and brain findings similar to those of the index case were identified over the interval 1991-2006; four of these had many aspects in common (Table 1). A fifth archival case with birth weight of 3368 g at 41 weeks survived 21 days. The lung showed massive superimposed lobular pneumonia and hemorrhage on 1+ bronchopulmonary dysplasia. There was gyromantle dysplasia with indistinct cortical layers, macrogyria, gliofibrillary meningeal nodules, bilateral narrow lateral dimension of basal ganglia, and far advanced fibrous septation of the thyroid with mixed collections of follicles typical of colloid goiter and others tightly compressed by the fibrosis. This case showed no remnant germinal matrix and was at term, suggestive of a major disturbance later in the migratory process. The greater maturity and prolonged survival prompted our determination not to include it in the table of principal cases.

In addition, a survey from the archives for 1983-2006 located 59 additional cases of bronchopulmonary dysplasia in 660 neonatal and infant autopsies (total database including stillborns, 1983-2006, 1280 autopsies with complete examination of the central nervous system), for a total of 71 (10.76 per cent). The proportion of cases of pulmonary fibrosis putatively affected by ABCA3 mutations, from this perspective, is a remarkable 16.9 per cent, not a trivial subset of infants. Eight additional cases of comparable cerebrocerebellar dystrophy, without lung fibrosis, were found in this survey. While a small number, it is sufficient to suggest the possibility of multigenic effects interrelating these lesions and susceptibilities.

DISCUSSION

This is a seeming case of first impression. The many complexities can be brought together as

a condition here designated as the **cerebropulmonary dysgenetic syndrome**, on a provisional basis.

Information now available in the medical and genetical literature makes it possible to establish

a connection between two severe pathological disorders in premature newborns:

1. Advanced and progressive pulmonary fibrosis, the late stage of hyaline membrane

   disease, well described as *bronchopulmonary dysplasia.*

2. Maturational discordance in the central nervous system, more especially migrational delay

   from the germinal matrix with neuronal underpopulation of the cortical mantle as a

   principal result. Associated is persistent paraventricular germinal matrix *per se*, with

   variable amounts of bulk migratory cells not far from their origin in the matrix, and, most

   remarkable, maturation of matrix *in situ.*

The link between these seemingly disparate devastations of key tissues in the newborn infant

lies with the demonstration of a ABCA3 heterozygotic mutant status in this case. ABCA3 is

one member of the ATP-binding casette transporter family A3, an important group of substance

transport molecules (Dean et al., 2001). Mutations in the ABCA3 gene have been identified as a

principal factor in fatal neonatal surfactant deficiency (Shulenin et al., 2004; Bullard et al., 2005).

Moreover, the ABCA3 mutants have been well characterized, classified, and localized in type 2

pneumocytes which produce surfactant, (Matsumura et al., 2006), thus setting the cellular stage for

the depletion of stored surfactant following the challenge of initial lung expansion (Bolande and

Klaus, 1964), with an inability to replenish the surfactant. In addition, LBM180, a lamellar body

limiting membrane protein of type 2 pneumocytes, has been identified as ABCA3 transporter protein

(Mulugeta et al., 2002). This finding solidifies the relationship of the protein to lung disorders common to premature newborns.

The link between the pulmonary disorder and the abnormal brain lies in some exacting work on the brain of the developing mouse which establishes an abundance of the ABCA3 protein in cortical mantle(Tachikawa et al., 2005), sometimes referred to in the fetal mouse as the differentiating zone. ABCA3 is also found throughout the early brain, but is not upregulated post natally in the white matter after the migration is completed (Tachikawa et al., 2005).

The superfamily of human ABC genes is complex with expression of *ABCA3* in lung and that of *ABCA2* in brain (Dean et al., 2001). *ABCA2* and *ABCA3* are closely related in subgroup ABCA-I (Dean et al., 2001). The ABCA3 sequence is highly conserved in humans, rats, and mice in the region of the E292V mutation (Bullard et al., 2005), enhancing the validity of applying the results of Tachikawa, et al (2005) in mice to the scope of disorders here described as the cerebropulmonary dysgenetic syndrome.

We have observed the unusual fibrous trabeculation of the thyroid occasionally but not systematically. Abnormal thyroid development and poor function were described in instances of global cerebral malformation by Shanklin (1991), offering the possibility of more than one factor at work in the endocrinopathy seen in our index case and in several from archival review.

The genetic mutation behind this pathogenesis has been attributed to an autosomal recessive state in a study on 12 newborns (Guala, et al., 2007). By contrast, another report of similar size

(Somaschini, et al., 2007), identified three of 14 as heterozygotic mutants [their patients 7, 8, and

13]. Bullard, et al. (2005), described three older individuals (ages 11, 16, and 23 years) with the

same missence mutation, E292V, found in our index patient, with a second mutation. These three

patients has interstitial lung disease at their much later stage of life (Bullard, et al., 2005). These

seeming discrepancies are evidence for compounded or multifactorial pathogenesis which may

include such counterintuitive results as an autosomal dominant variant of the Wiskott-Aldrich

syndrome, classically understood to be an X-linked recessive disease (Rocca, et al., 1996). It may

be that certain regulatory proteins have to present in both parental genomes for proper function in

the offspring. A variant allele through mutation can be sufficient to create an abnormal phenotype

in that the haploid state of the wild type allele is inadequate for normal function. This is the case for

a number of disorders. Women with heterozygous α-galactosidase mutations (Fabry disease) suffer

from significant multisystemic disease, resulting in a reduced quality of life (Wang, et al., 2007).

Wang and associates studied 44 heterozygous women, a majority referred due to an affected male

relative, of whom about 75% reported acroparesthesias as their first symptom (Wang, et al., 2007).

Other symptoms were prominent such as fatigue with reduced oxygen consumption, exercise

intolerance with low heart rate during exercise testing, and angina, symptoms characteristic of the

homozygous state (Wang, et al., 2007). Comparable confounding heterozygotic abnormalities have

been described for familial hypobetalipoproteinemia (Alapont Puchalt, et al., 2004). Perhaps the

best example of enhanced risk for disease manifestations from the heterozygous mutant state is

factor V Leiden (Glueck, et al., 2007; Herman, et al., 2006; Imperiale, et al., 2007;Kalajian, et al.,

2007; Marchiori, et al., 2007; Verdu, et al., 2005). Marchiori, et al. (2007) estimated risk ratios

on the order of 1.39 to 1.45, which, considering the tendency for this trait to become manifest in

pregnancy, is an important health problem. At a fundamental cellular level, DNA polymerase β, carries out base excision repair necessary for DNA maintenance (Bhattacharyya and Banerjee, 1997). A variant polymerase from deletion in the 87-bp region, in the heterozygous state, results in cells incapable of base excision repair and highly sensitive to the known group 2A animal carcinogen, N-methyl-N'-nitro-N-nitrosoguanidine (Bhattacharyya and Banerjee, 1997; Fujii and Nakadate, 1977).

The index case in this report serves to suggest more frequent genetic testing in the clinical scenario of early bronchopulmonary dysplasia in premature newborns will provide necessary data by which to assess the prevalence of this potential complication of neonatal care. The archival cases reported here are a window onto new aspects of development of the human fetal brain. There are now four well documented examples of severe bronchopulmonary dysplasia related to heterozygous mutations in the ABCA3 transporter protein gene (Somaschini, et al., 2007 and this case). The existence of an increasing number of instances where the heterozygous state carries significant risk burdens (as cited above) is a compelling argument for further study and clarification of the risk and the processes by which these disorders are manifested.

Author's statements

Total word count (including these lines) of text, references, and legends = 3660
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LEGEND FOR TABLE

Table 1: Comparison of findings, index and archival cases.

LEGENDS FOR FIGURES

All photographs are of tissues stained by hematoxylin and eosin; original magnifications, 100X.

Figure 1: Representative pulmonary lobule with extensive advanced fibrosis, mononuclear cell

proliferation, and disordered vascular pattern. There are no competent peripheral

air spaces and rare terminal bronchioles (not shown). This pattern was found

throughout all five pulmonary lobes.

Figure 2: Paraventricular germinal matrix, midzone, with irregular remnant clusters of primitive

glioneuroblasts mingled with neural cell maturation *in situ*. Similar masses of immature

migratory cells were *in stasis* adjacent to and occasionally surrounding blood vessels

in the influence of the middle cerebral arteries.

Figure 3: Representative zone of parietal motor cortex. Layers of the cortical mantle are poorly

arrayed; the locus of layer 5, across the middle of the view, lacks defined

pyramidal and protopyramidal neurons. These are usually conspicuous by 30-31 weeks

gestational age.

Figure 4: Thyroid gland marked by dense interlacing fibrous septa which surround poorly

developed follicles lacking colloid normally present at a gestational age of

34 weeks.

Table

Case	Index	Archive-1	Archive-2	Archive-3	Archive-4
Gestation	34 weeks	26 weeks	25 weeks	32 weeks	28 weeks
Birth Wt.	1770 g	699 g	620 g	951 g	942 g
Survival	8.3 days	10.0 days	26 days	18 days	57 days
Lung	4+ fibrosis	4+ fibrosis	4+ fibrosis, leimyomatosis	1+ with remnant hyaline membranes and infarcts	2+ with superimposed necrotizing pneumonia
Germinal matrix delay	Marked, extensive	Little migration beyond GM	GM hemorrhage and rupture	Gliofibrillary nodules, clusters	Remnant almost without migration
Cortical mantle	Poorly layered, underpopulated	Much retarded, focal dysplasia	Retarded, zones of discordancy	Immature, no layer 5 neurons	Cortical dysplasia and poor layers
Thyroid	Dense fibrous septation	Fibrocystic dysplasia	Slow development	No lesion recorded	No lesion recorded
Adrenal	Small, medullary maturity, adenoma next to capsule	Neural crest delay	Adrenal rest in hilum of testis	Slow post natal involution, fetal zone	Fetal cortical involution complete for age
Pituitary	Eosinophilia	Eosinophilic nodule	Normal for age	Normal for age	Normal for age