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On the curious association of diaphragmatic hernia and Urban-Rifkin-Davis Syndrome (Autosomal Recessive Cutis Laxa-1C): A collective review of 16 cases

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KEYWORDS

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ABSTRACT

Background: Autosomal recessive cutis laxa type-1C is also known as Urban-Rifkin-Davis syndrome (URDS). It is known to affect cardiopulmonary, integumentary, gastrointestinal, musculoskeletal and genitourinary systems. However, its frequent association with congenital diaphragmatic hernia has not previously been highlighted.

Case Presentation: A newborn male with cutis laxa presented with respiratory distress at birth. The cause of dyspnoea was perinatal strangulation of the stomach in hiatus hernia. After surgical repair of the hernia, his respiratory distress temporarily improved but kept recurring periodically by various mechanisms in sequence namely pulmonary hypertension, tracheomalacia, pulmonary emphysema and finally he succumbed to pneumothorax. Genetic analysis revealed his skin condition as autosomal recessive cutis laxa type-1C which is also known as URDS. Exome sequencing revealed a novel frameshift mutation c.426delC (p.Cys143Alafs*41) of the LTBP4 gene in the exon 5 of Chromosome 19.

Conclusion: Out of the 28 cases of URDS reported in the world literature 57% had congenital diaphragmatic hernia (CDH) and 53% of them died during infancy. Such a high incidence of CDH is not observed in other subtypes of elastic disorders. Thus, congenital diaphragmatic defects appear to be a characteristic diagnostic feature of URDS in patients with cutis laxa.

INTRODUCTION

Cutis laxa (CL) is a systemic disorder characterized by abnormal elastic fibers in connective tissues. [1] The term CL is a misnomer because this disorder affects not only the skin but also all other internal organs. Premature senile look caused by hypo-elastic sagging skin is a characteristic phenotype of this disorder. CL may be acquired or congenital, the later may be of autosomal (dominant or recessive) or X-linked inheritance. Congenital CL is classified into 10 overlapping subtypes based on the pattern of inheritance, predominantly affected organ systems and clinical manifestations. [2] Among them, autosomal recessive cutis laxa type-1C (ARCL-1C) is also known as Urban-Rifkin-Davis syndrome (URDS). [3, 4]

Since its first description in 2009, only 27 cases of URDS have been documented in the world literature. [4-13] (Table 1) URDS is caused by mutation of the gene for Latent Transforming Growth Factor-β Binding Protein-4 (LTBP4). [14] This syndrome is characterized by predominant involvement of pulmonary, gastrointestinal, genitourinary, musculoskeletal and dermal systems. While reviewing the world literature for the management of a newborn with URDS, we noticed that in contrast to other types of cutis laxa, URDS is more frequently complicated by congenital diaphragmatic hernia (CDH). This curious association has not previously been highlighted.

CASE REPORT

A 2-day-old male newborn was admitted with severe respiratory distress at birth and inability to pass a nasogastric tube during resuscitation. He was born to second-degree consanguineous parents at full-term by cesarean section. He weighed 3.7 kg and his birth Apgar score was 6 out of 10. His parents and an elder female sibling aged 5-years were healthy without any phenotypical abnormalities.

On admission his respiratory rate was 83/min and SpO2 was 84%. With oxygen supplementation, SpO2 improved to 93% but tachypnoea persisted. Breath sounds were diminished in the left hemithorax. The

skin was universally lax, redundant and inelastic. (Fig.1) He also had other dysmorphic features such as hypertelorism, micrognathia, low-set ears, receding forehead, prominent nose, short neck, coarse cry and generalized muscular hypotonia. However, cyanosis, stridor, cardiac murmurs, inguinal or umbilical hernia, vomiting, joint laxity and hair abnormalities were absent.

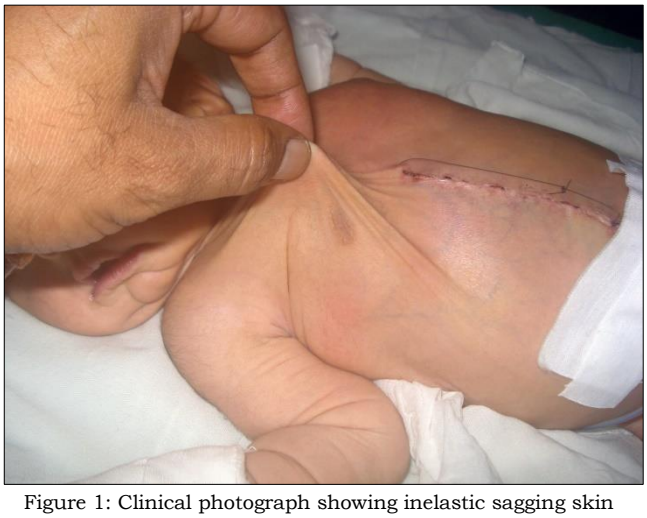

Figure 1: Clinical photograph showing inelastic sagging skin

Imaging studies confirmed strangulated para-esophageal (hiatus) hernia of rolling type as the cause of respiratory distress. (Fig. 2) Ultrasonography of abdominal organs was grossly normal. In view of his critical condition, further imaging such as gastrointestinal contrast study and voiding cystourethrography were not done.

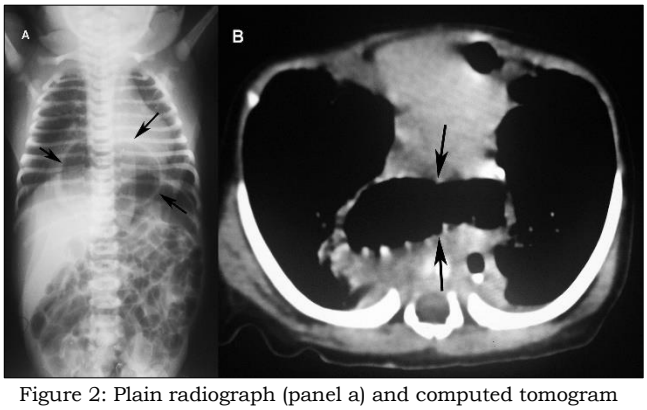

Figure 2: Plain radiograph (panel a) and computed tomogram (panel b) showing herniated stomach through the esophageal hiatus (arrows).

On day-3 of life he successfully underwent open surgical repair of hiatus hernia under general anesthesia. Entire stomach that had herniated into the chest was reduced and the defect of the esophageal hiatus was repaired. Post-operatively, respiratory distress temporarily improved only to recur on day-7. Echocardiography showed four-chamber dilatation with moderate mitral regurgitation and pulmonary hypertension (PHT). Following administration of Sildenafil (1mg/kg bd), PHT and respiratory distressed resolved completely. He was discharged asymptomatic on post-operation day-15.

After 3 months, he was readmitted with respiratory distress. Echocardiography did not reveal any PHT but dilated cardiomyopathy persisted. There was no recurrence of hiatus hernia. On parental request, he was transferred to another hospital for detailed evaluation of cardiomyopathy and suspected tracheomalacia. Imaging studies done at the referral center was reported to show bilateral pulmonary emphysema. Unfortunately, he was said to have died of pneumothorax while attempting central venous access for cardiac studies.

Genetic Studies

On the 7th post-operation day, after obtaining informed parental consent, genetic diagnosis of his disorder was performed on genomic DNA extracted from leukocytes. Sequencing of the protein coding regions approximating 30Mb of the human exome (targeting approximately 99% of regions in consensus coding sequence-CCDS and reference sequence-RefSeq databases) was performed using Illumina Next Generation Sequencing systems at a mean depth of 80-100X. Percentage of bases covered at 20X depth was >90% in the targeted region. Genomic Analysis Toolkit (GATK) best practice framework was followed for variant identification. BWA-mem aligner was used to align the obtain sequences to human reference genome (GRCh37/hg19). Base quality recalibration and re-alignment of reads based on indels were done using inbuilt Sentieon module. Sentieon's Haplotype-caller module was used to identify variants which are clinically relevant. Variant annotation was done using published databases like Online Mendelian Inheritance in Man (OMIM), Genomewide association Study (GWAS), Genome Aggregation Database (GnomAD) and 1000-Genome project. Non-synonymous and splice site variants were used for clinical interpretation.

Results of Genetic Studies

Targeted exome analysis revealed homozygous frameshift deletion variant, c.426delC (p.Cys143Alafs*41) in exon 5 of the LTBP4 gene on the chromosome 19q13. It occurred in an exon of LTBP4 upstream where nonsense mediated decay is predicted to occur. There were 5 downstream pathogenic loss-of-function variants, with the farthest variant being 1229 residues downstream. This mutation has not been previously reported in the literature. (Table 1) The mutation is found to be conserved across the species by GERP (Genomic Evolutionary Rate Profiling) or Phylop scores and it is predicted to be of damaging nature by Combined Annotation Dependant Depletion (CADD)/Mutation Taster. As the variant is a low rate, benign loss of function variant, as per American College of Medical

Genetics guidelines, it is classified as 'likely pathogenic' for URDS (OMIM 613177).

The proband also had a heterozygous missense variant c.947C>T (p.Thr316Met) at exon 6 of the DCPS gene (NM_014026.6) on the chromosome 11q24 which is considered to be 'pathogenic' or 'likely pathogenic'. Thus, the proband is known to be a carrier of Al-Raqad syndrome (OMIM 616459). No other pathogenic variants or copy number variations were identified.

DISCUSSION

Autosomal recessive cutis laxa (ARCL) is divided into 6 subtypes (1A, 1B, 1C, 2A, 2B and 3) based on the nature of defective genes and altered protein synthesis. [1,2] For example, ARCL-1A is caused by mutation of fibulin-5 gene (FBLN5), ARCL-1B by FBLN4 and ARCL-1C by LTBP4. Despite considerable overlapping of clinical features, each subtype is clinically distinct affecting a specific set of organ systems. For example, corneal opacity is characteristic of ARCL-2B and ARCL-3 but not other subtypes. [1] Similarly, we noted a peculiar association between URDS and congenital diaphragmatic hernia (CDH) which has not previously been highlighted. A comprehensive review of the world literature revealed that 16 (57%) out of the 28 cases of URDS were associated with diaphragmatic defect. (Table 1)

CDH is well known to occur in 20-25% of hyperelastic syndromes such as Marfans and Ehlers-Danlos. [15,16] But its specific association with hypoelastic (elastolytic) disorders such as cutis laxa has not previously been emphasized. None of the major reviews on this topic recognize this curious association. [17-20] Among the patients of cutis laxa, CDH has also been reported in ARCL-1A and ARCL-1B; but the frequency seldom exceeds 10%. [4] Thus, the high frequency of 57% makes CDH a characteristic clinical feature of URDS.

Congenital diaphragmatic hernias are of three types based on the anatomical location of the defect: they are Bochdaleck hernia (postero-lateral), Morgagni hernia (substernal) and hiatus hernia (para-esophageal). Eventration is another form of herniation which is caused by generalized laxity of diaphragm without any localized anatomical defect. Although all of them are known to occur in URDS, para-esophageal hiatus hernia (37%) and diaphragmatic eventration (44%) predominate. (Table 1).

The exact mechanism as to how genetic mutations influence diaphragmatic defects is not known. Defective genes are known to cause synthesis of abnormal proteins and hence altered physiology. TGF-β is a growth factor that is essential for the development of vascular endothelium (vasculogenesis) and elastic fibers in extracellular matrix (elastogenesis). [20,21] Defective LTBP-4 affects the integrity of elastic fibers through TGF-β. In the absence of stable extracellular elastic fibers, migration of mesenchymal (myotome) cells during embryogenesis is severe affected thereby causing defective musculature of the diaphragm and defective alveolarization of lungs. In addition to LTBP-4 gene, more than 2 dozen genes such as FBN1, FBLN4 and FBLN5 also take part in normal elastogenesis. [19-21] We hypothesize that the nature of gene mutations might be responsible for site-specific elastic deficiency. This may explain the high frequency of CDH in URDS as compared to other varieties of CL. Not only the topography of diaphragmatic defect but also its degree of severity and co-morbidities are now known to be associated with genetic mutations. [20] Accumulated knowledge of all genetic mutations, including novel one as reported in this paper, will expand our understanding of the curious association of CDH and URDS

As cutis laxa affects the connective tissue of all organ systems, cause of respiratory distress is diverse. [20] Lack of tissue elasticity is the basic pathogenic mechanism common to all of them. Dyspnoea may be due to laryngo-tracheo-broncho-malacia, emphysema of lungs, pulmonary hypertension due to inelasticity of the pulmonary artery, dilated cardiomyopathy, incompetence of cardiac valves, cardiac septal defects, weakness (hypotonia) of respiratory muscle, aspiration pneumonia due to esophageal dysmotility and diaphragmatic hernia. (Table 1) More importantly the cause of respiratory distress in the same patient may change over time. This phenomenon is well demonstrated in our patient who developed diaphragmatic hernia, pulmonary hypertension, laryngomalacia, cardiomyopathy, emphysema and pneumothorax sequentially over a period of 3 months. Therefore, it is imperative to evaluate the underlying cause of respiratory distress afresh during each episode of dyspnoea as well as when expected clinical progress does not occur with proper treatment.

Nearly 53% of patients with URDS develop lethal respiratory distress during early infancy. The longest survivor was of 20-years age. [6] Several therapeutic interventions have been theoretically proposed in URDS but none were clinically tested. They include tracheal stenting for tracheo-bronchomalacia, pulmonary vasodilators for PHT, digoxin for dilated cardiomyopathy and cardiac valve replacement. In our case respiratory distress due to PHT temporarily resolved with Sildenafil (a pulmonary vasodilator) only to return by a different mechanism (emphysema).

Table 1. Clinico-genetic correlation of Diaphragmatic hernia and respiratory distress in Urban-Rifkin-Davis Syndrome

Sr. No	Author (year)	Genetic abnormality						Diaphragmatic hernia	Respiratory distress		Clinical outcome
		Exon	Domain	Zygocity	Mutation type	cDNA change	Protein change		Age at onset	Other risk factors of dyspnoea	
1	Urban (2009)	28	8-Cys 2	Homo	FS-PTC	c.3554delA	p.Q1185fsX1211	None	2 months	PAH/s, RVH, aspiration pneumonia due to esophageal dysmotility, pulmonary stenosis, emphysema, ASD, general muscular hypotonia, retrognathia	Died at 9 months
2	Urban (2009)	9	Hybrid	Hetero	FS-PTC	c.791delC	p.264fsX300	Eventration	7 weeks	Laryngo-tracheo-bronchomalacia, emphysema, ASD, general muscular hypotonia, retrognathia	Died at 4 months
		22	EG 11	Hetero	Nonsense	c.2570_2571delGCinsAA	p.C857X				
3	Urban (2009)	9	Hybrid	Homo	Missense	c.820T>G	p.C274G	Para-esophageal + Substernal recurrence at 3yr	At birth	Aspiration pneumonia due to GERD, retrognathia	Alive at 7 years
4	Urban (2009)	22	EG 11	Hetero	Nonsense	c.2570_2571delGCinsAA	p.C857X	Postero-lateral	3 months	Viral pneumonia, PHT, tracheomalacia, emphysema, muscular hypotonia, retrognathia	Died at 23 months
		33	8-Cys 3	Hetero	FS-PTC	c.4128insC	p.P1376fsX1403				
5	Callewaert (2013)	11	8-Cys 1	Hetero	Nonsense	c.1342C>T	p.Arg448X	Unspecified type	Not specified	Emphysema, pulmonary artery stenosis,	Alive at 23 years
		31	8-Cys 3	Hetero	FS-PTC	c.4115dupC	p.Tyr1372Ilefs*2				
6	Callewaert (2013)	19	EG 7	Homo	Nonsense	c.2408C>A	p.Ser803X	None	Not specified	Emphysema, laryngo-tracheomalacia, PAH	Died at 4 weeks
7	Callewaert (2013)	28	8-Cys 2	Hetero	Nonsense	c.3661C>T	p.Gln1221X	None	Not specified	Emphysema	Died at 3 months
		29	EG 14	Hetero	Nonsense	c.3886C>T	p.Gln1296X				
8	Callewaert (2013)	6	-	Homo	Splice Site	c.780+2T>G	ND	Unspecified type	Not specified	Emphysema, PAH	Died at 2 years
9	Callewaert (2013)	11	8-Cys 1	Homo	FS-PTC	c.1263delC	p.Cys422Alafs*352	Unspecified type	Not specified	Emphysema, ASD, CVI	Died at 10 years
10	Callewaert (2013)	15	EG 2	Homo	Nonsense	c.1851C>A	p.Cys617X	None	Not specified	Emphysema , PHT,	Died at 6 months
11	Callewaert (2013)	31	8-Cys 3	Homo	FS-PTC	c.4127dupC	p.Arg1377Alafs*27	Unspecified type	Not specified	Emphysema , PHT, ASD, PAH, cardiac valve insufficiency	Died at 6 months
12	Callewaert (2013)	31	8-Cys 3	Homo	Nonsense	c.4129C>T	p.Arg1377X	None	Not specified	Emphysema, PAH, PHT	Died at 13 years
13	Callewaert (2013)	26	8-Cys 2	Homo	Missense	c.3556T>C	p.Cys1186Arg	Para-esophageal	Not specified	Emphysema, ASD, PHT, CVI	Died at 6 weeks
14	Su (2015)	7	Hybrid	Hetero	-	c.883+1G>T	ND	Unspecified type	At birth	Hypotonia, emphysema, PAH, CVI, PDA, ASD	Died at 15 months
		17	EG 8	Hetero	-	c.2161C>T	p.R721*				
15	Su (2015)	18	EG 9	Hetero	-	c.2377_2378insA	p.G793Efs*5	Para-esophageal	-	Asthma, PAH, pericardial effusion, CVI, obstructive lung disease, scoliosis	Alive at 14 years

		29	EG 18	Hetero	-	c.3856T>A	p.C1286S				
16	Su (2015)	20	EG 11	Hetero	-	c.2632 G>T	p.G878*	None	Not specified	RV hypertrophy, PAH, PHT	Alive at 20 years
		31	8-Cys 3	Hetero	-	c.4113dupC	p.A1372Rfs*3				
17	Su (2015)	5	EG 1	Homo	-	c.341-1G>C	ND	Para-esophageal	Not specified	Right heart failure, pneumonia, hypotonia, esophageal divertivula, VSD, PAH	Died at 6 weeks
18	Ritelli (2019)	12	-	Homo	FS-PTC	c.1450del	p.Arg484Glyfs*290	Eventration	Perinatal	Hypotonia, ASD, pneumonia, esophageal dysmotility	Alive at 18 months
19	Gupta (2020)	1	-	Homo	FS-PTC	c.145_163delCCGACCGGCTCCCGCTGTA	p.Thr50ArgfsTer31	None	None	Emphysema, hypotonia, CVI	Alive at 8 years
20	Gupta (2020)	1	-	Homo	FS-PTC	c.145_163delCCGACCGGCTCCCGCTGTA	p.Thr50ArgfsTer31	None	None	Emphysema	Alive at 4 years
21	Melo (2020)	-	-	Homo	Splice site	c.780+2T>G	ND	Unspecified type	None	PAH, ASD, CVI, hypotonia	Alive at 4 months
22	Albayrak (2020)	28	EG Ca^{++} binding site	Homo	Missense	c.3740A>G	p.N1247S	None	None	PAH, Bronchitis, pneumonia	Alive at 5 years
23	Albayrak (2020)	5	TB	Homo	-	c.2T>G	p.M1R	Unspecified type	Not specified	Bronchitis, emphysema, DCM, CVI	Alive at 7 years
24	Albayrak (2020)	5	TB	Homo	-	c.2T>G	p.M1R	None	At birth	CVI, ASD, Pneumothorax	Died on day 58
25	Zhang (2020)	-	-	Hetero	FS-PTC	c.605_606delGT	p.Ser204fs*8	None	None	Pneumonia, emphysema, ASD	Alive at 28 days
		-	-	Hetero	FS-PTC	c.1719delC	p.Arg574fs*199				
26	Mazaheri (2022)	6	-	Homo	Splice site	c.533-1G>A	ND	Para-esophageal	At birth	PAH, DCM, ASD	Alive at 40 weeks
27	Ravel (2022)	30	EG 14	Homo	In-frame deletion	c.3774-3782del	p.Asp1259-Asp1261del	None	17 months	Pectus excavatum, PAH, emphysema	Alive at 17 months
28	Present study	5	-	Homo	FS deletion	c.426delC	p.Cys143Alafs*41	Para-esophageal	At birth	Emphysema, PHT, hypotonia, DCM, tracheomalacia, CVI	Died at 3 months

8-CYS-8-cysteine domain; ASD – Atrial septal defect; CVI – Cardiac valve incompetence; DCM – Dilated cardiomyopathy; EG-Epidermal growth factor-like domain; FS-Frame-shift mutation; GERD – Gastroesophageal reflux disease; ND-Not determined/described; PAH/s – Pulmonary artery hypoplasia / stenosis; PHT- Pulmonary hypertension; PTC-Premature truncation of codon; RVH – Right ventricular hypertrophy; TB – Transforming growth factor β binding protein-like domain; VSD – Ventricular septal defect.

The basic molecular defect of URDS is altered protein binding of Transforming Growth Factor-β (TGF-β) which leads to abnormal synthesis of elastin fibers. [14,21] Losartan, an angiotensin-II type-1 receptor antagonist, has been found capable of modifying the TGF-β signaling. [22] Therefore, Urban et.al hypothesized that losartan or neutralizing monoclonal antibodies against TGF-β may prevent visceral malformations or malfunctioning in URDS. [2,3] The novel mutation reported herein may be useful in designing such targeted molecular therapy, genetic screening and clinical diagnosis.

In conclusion, out of the 28 cases of URDS reported in the world literature 57% had congenital diaphragmatic hernia (CDH) and 53% of them died during infancy. Such a high incidence of CDH is not observed in other subtypes of elastic disorders. Thus, congenital diaphragmatic defects appear to be a characteristic diagnostic feature of URDS.

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