Chest Computed Tomography Findings in Familial Dysautonomia Patients: A Model for Aspiration

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ABSTRACT: **Background:** Lung disease in patients with familial dysautonomia is caused mainly by recurrent aspiration of gastric contents, food and liquids swallowed incorrectly.

Objective: To describe chest computed tomography findings in patients with familial dyautonomia.

Methods: A retrospective analysis of chest CT findings was performed for 34 FD patients (15 females, 19 males) with a mean age of 18 ± 12.8 years.

Results: The CT revealed bronchial wall thickening (in 94% of the patients), atelectasis (in 73%), ground glass opacities (in 53%), focal hyperinflation (in 44%), fibrosis (in 29%) and bronchiectasis (in 26%). The extrapulmonary abnormalities were scoliosis (79%) and esophageal dilatation (35%). Silent fractures were noted in two vertebral bodies and one rib.

Conclusions: Pulmonary changes were consistent with chronic inflammation in the bronchi and interstitial tissues. Ground glass opacities and fibrosis support the theory that these changes could be due to gastric aspiration. Bronchiectasis is less frequent. Esophageal dilatation with fluid overflow adds to aspiration. Fractures can be asymptomatic and are often missed.

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KEY WORDS: chest CT, familial dysautonomia, Riley-Day syndrome, aspiration, ground glass opacities

Familial dysautonomia, also known as Riley-Day syndrome, is a hereditary autosomal recessive disorder characterized by autonomic and sensory dysfunction. It has been observed almost exclusively in individuals of Eastern European Jewish descent, in whom the incidence is 1:3703 [1]. The FD gene was discovered in 2001 [2]. In FD there is underdevelopment of peripheral unmyelinated and small myelinated neuronal fibers, as well as a decreased number of neurons in autonomic and sensory ganglia [1,2].

Abnormal autonomic neuronal development results in disturbed neuroregulation of most organ systems. The defective function includes the cardiovascular, respiratory, gastrointestinal and skeletal systems. Body temperature regulation and pain response may also be altered. There is an absence of overflow tears. Stress may lead to FD crisis response, which is manifested by bouts of vomiting, hypersalivation, high blood pressure, sweating, blotching, and behavioral changes. Recurrent respiratory distress episodes are common due to chronic aspiration and recurrent lung infections. Central and obstructive apnea events occur during sleep [2].

Pulmonary manifestations are the main cause of morbidity and mortality. Acute respiratory events are usually evaluated with chest X-ray; however, chest computed tomography is often performed to obtain a more detailed evaluation. FD is a well-documented clinical condition that can serve as a model for lung disease secondary to recurrent aspirations from either fluid or food introduced by mouth or aspiration of gastric content from gastroesophageal reflux. Very few data have been published concerning the radiological, and especially chest CT manifestations in FD [3,4]. To our knowledge this is the first study describing the spectrum of manifestations in FD on chest CT.

PATIENTS AND MATERIALS

All thoracic CT scans of 34 FD patients, who were followed and treated from January 1997 until June 2007 in an FD center, were retrospectively evaluated. The diagnosis of FD was established by clinical signs and symptoms and by genetic testing. There were 15 females and 19 males in the series. Patient age ranged from 2 months to 50 years (mean 18 years ± 12.8 SD). Institutional review board approval was not required for this study.

All FD patients included in the study had a history of episodes of choking while drinking or eating, as well as GER and recurrent pneumonia. They were referred for chest CT evaluation due to worsening of respiratory symptoms, including decreased oxygen level (< 90 mmHg) and increased carbon dioxide level (> 48 mmHg), or for the evaluation of new markings on chest X-rays.

Chest CT examinations were performed on one of the following commercial CT scanners: Helical Twin Flash Scanner (Philips, Eindhoven, The Netherlands), Helical 4-slice MX 8000 scanner (Philips), and GE-Lightspeed 16-slice scan-

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FD = familial dysautonomia

GER = gastroesophageal reflux

ner (General Electric Medical Systems, Milwaukee, USA). Standard scan parameters for chest CT were used, including both 3.75–5 mm and high resolution 1–1.25 mm slice thickness. All chest CT scans were obtained in a single breath hold during suspended end-inspiration in the supine position. Intravenous contrast material was used in a few studies. Lung, mediastinal and bone windows were reviewed.

All chest CT scans were retrospectively reviewed independently by two board-certified experienced radiologists who are experts in chest radiology. Cases of observers' disagreement were resolved by consensus.

Parenchymal, bronchial, pleural, mediastinal and skeletal abnormalities were assessed. Presence or absence, and pattern of distribution of parenchymal changes were evaluated, including ground glass opacities, tree-in-bud opacities, nodules, parenchymal bands, consolidations, bronchiectasis, peribronchial inflammatory changes, reticulation, and focal areas of hypoattenuation. All changes were noted and located in accordance with the definitions of the Nomenclature Committee of the Fleishner Society [5]

Bronchial walls that were visually thicker than the corresponding bronchus of the same caliber on the contralateral lung, or other bronchi of the same caliber in the same lung on a cross-sectional image of the bronchus were considered thickened. Atelectasis was classified as segmental or subsegmental. Pulmonary arterial enlargement was diagnosed when the diameter of the main pulmonary artery exceeded that of the ascending aorta. Tracheomegaly was defined as transverse trachea diameter over 2 standard deviations larger than the Griscom measure [6] in patients under the age of 18, > 2 cm in adult females and > 2.5 cm in male adults. Other extrapulmonary changes were evaluated, including pleural and pericardial effusion, mediastinal or hilar lymphadenopathy, dilatation of the stomach or esophagus, and diaphragmatic hernia. Given the possibility of occult fractures, attention was paid to bone structures. The angle of scoliosis was measured and the side of its curvature was registered. Scoliosis was graded as mild (< 20 degrees), moderate (20–40 degrees) and severe (> 40 degrees). Pulmonary function tests were not included since most FD patients have poor coordination and compliance and this test is therefore not reliable.

Table 1. Chest CT findings in 34 FD patients

Radiological manifestations	No. of patients (%)
Bronchial wall thickening	32 (94)
Atelectasis	25 (73)
Ground glass opacities	19 (56)
Focal air trapping	15 (44)
Parenchymal bands	10 (29)
Reticulation	8 (23)
Bronchiectasis	9 (26)
"Tree-in-bud" bronchial changes	6 (18)
Nodules	5 (15)
Consolidation	3 (9)
Lymphadenopathy	2 (6)
Pulmonary hypertension	5 (15)
Esophageal dilation	12 (35)
Diaphragmatic hernia	6 (18)
Scoliosis	27 (79)

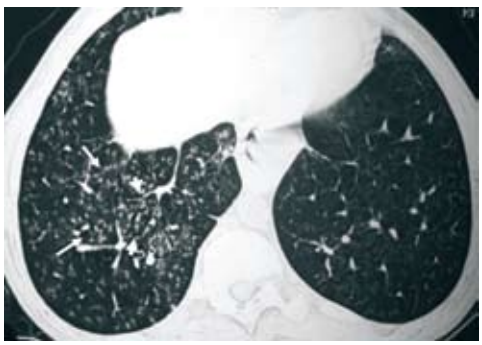
RESULTS

Pathological chest CT findings were observed in all FD patients [Table 1]. The most common pulmonary findings were bronchial wall thickening (in 94%, mean age 21 years old) and atelectasis (73%, mean age 19). Changes were mostly diffuse and bilateral with no lobar predominance. Atelectasis was either segmental (56%) or subsegmental (44%), with no zonal predilection.

Small airway inflammatory changes with exudative bronchiolar, tree-in-bud dilation [Figure 1] were seen only in the lower lung fields (6%, mean age 13). Bronchiectases (26%, mean age 21) were cylindrical, with no zonal predominance [Figure 2]. Areas of decreased attenuation, without zonal distribution (44%, mean age 19) and ground glass opacities (56%, mean age 21), with a diffuse asymmetric and peripheral distribution, were common. Pulmonary nodules (15%, mean age 23) were usually peripheral [Figure 3]. Reticulation (23%, mean age 15) was at a peripheral and basilar distribution. Irregular linear opacities (bands) were present in 29% of the patients (mean age 28), usually mild (80%). Three cases of lung consolidation probably represented ongoing pneumonia. In the majority of patients a combination of changes was seen on CT.

Pulmonary arterial enlargement was seen in 14.7% of patients ranging in age from 5 to 50 (mean 24 years). Pulmonary hyper-

Figure 1. An axial CT through lung bases of a 24 year old female patient with FD shows bronchial wall thickening and diffuse tree-in-bud appearance (arrows) predominately in the right lung. Parenchymal bands are also present (arrowheads). Hyperinflation is noted at the left lung base. Note the mild scoliosis.



tension was confirmed on electrocardiography and echocardiogram in these patients. Pleural effusion was found in only one patient, aged 49. Pleural thickening was noted in one patient and tracheomegaly in two.

Scoliosis was common (80%) and was right sided in 63% and left sided in 37% of the cases. Scoliosis presented in varying degrees of severity and ranged between 7 and 80 degrees. The degree of scoliosis (see Methods) was mild in 8 patients, moderate in 10 and severe in 9. There was no direct correlation between the degree or scoliosis side and the distribution or severity of pulmonary changes. Esophageal dilation (35%) had no correlation to the degree of scoliosis. Two patients had mild esophageal compression between the aorta and the scoliotic spine. Three fractures, two vertebral and one costal, were found in patients with osteopenia, with extensive callus. None of these patients had recalled any specific complaints related to the fracture.

DISCUSSION

Familial dysautonomia is a severe and complex disease that affects most of the body systems. The rates of morbidity and mortality are high, mostly due to pulmonary complications following recurrent aspirations [2]. FD patients have sucking and eating difficulties. Recurrent food and fluid aspiration is common and is attributed to several factors, including lack of coordination in the nasopharyngeal area as well as GER. In addition, FD patients suffer from FD crises, with associated recurrent bouts of vomiting and hypersalivation, which also can lead to aspiration. All these factors can lead to recurrent bronchopneumonia and subsequent chronic pulmonary changes [2,7,8].

Previously described radiological findings based on chest X-rays included interstitial infiltrates, atelectasis, emphysema, peribronchitis and chronic bronchopneumonia [3,4]. However, chest CT has been shown to be superior to chest X-ray in depicting lung abnormalities.

Atelectasis, which was common in our study group, can be explained by airways obstruction due to food or liquid aspiration, GER, or secretions, as well as bronchial inflammation and subsequent wall thickening. Other pulmonary changes were consistent with chronic or recurrent airways disease, presented as bronchial wall thickening and tree-in-bud changes. However, bronchiectasis was not as frequent as expected. Lung nodules can also be attributed to bronchial wall thickening and peribronchial inflammatory changes. The incidence of lymphadenopathy in our study was low.

We found a high rate of ground glass opacities, presumably secondary to focal hypoaeration resulting from airway disease and chronic interstitial inflammation and fibrosis. Focal areas of decreased parenchymal attenuation can also be attributed to inflammation and small airway obstruction, resulting in increased vascular resistance and subsequent hypoperfusion.

Reticulation and parenchymal bands most probably represented chronic interstitial disease and fibrotic changes secondary to recurrent pulmonary aspirations with chemical irritation by gastric acid and food, with subsequent infection. The relationship between pulmonary fibrosis and GER has been described [7,9]. The effects of acid on the lungs has been examined in animal studies [10], which showed that alveolar injury was due to chemical pneumonitis followed by interstitial fibroblastic proliferation and pulmonary fibrosis [10,11]. Alveoli and alveolar duct collapse, resulting in adherence of septa to the ductal wall and an exaggerated inflammation, have also been described [12]. An exaggerated inflammatory response during pneumonia and increased bacterial adherence in aspiration were demonstrated in animal models [13,14]. Hydrochloric acid aspiration was

Figure 2. CT through the mid-thorax of a 15 year old male with FD shows ground glass opacities at the apical segment of the right lower lobe (black arrowheads), bronchial wall thickening and bronchiectasis in the right and left upper lobes (white arrows), and diffuse hyperinflation and vascular attenuation, especially in the right upper lobe (black arrows).

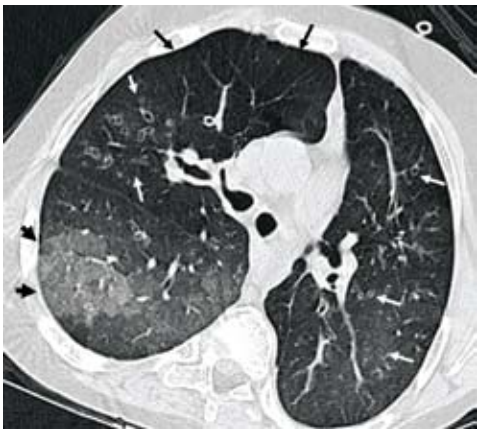
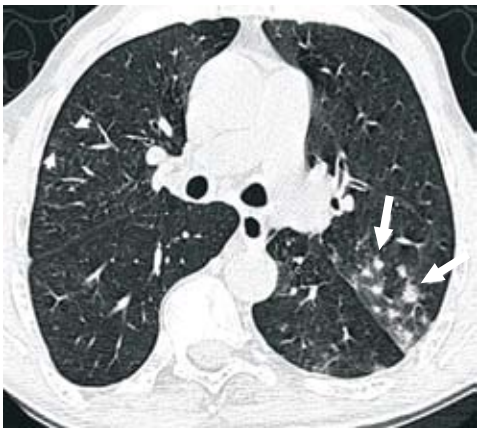


Figure 3. CT at the subcarinal level in an 18 year old male patient with FD shows multiple ill-defined lung nodules at the posterior aspect of the left upper lobe (arrows), representing small airways wall thickening or mucous plugging. Mild peripheral bronchiectasis is seen in the right upper lobe (arrowheads). Note the mild scoliosis.



shown to cause aspiration pneumonitis and increased release of pro-inflammatory mediators on stimulation with *Klebsiella* lipopolysaccharide [14]. Acid-injured epithelium also increases *Pseudomonas aeroginosa* adherence, and may explain the severity of bacterial pneumonias in patients with aspiration of gastric contents [13].

Other investigators [15,16] found that GER incidence was significantly higher in patients with radiological evidence of pulmonary fibrosis, as compared with controls. Thus, GER could explain the high incidence of fibrotic changes in our FD patients. Raiha et al. [17] studied the relationship between GER and radiological changes and found a significant increase in bilateral pleural adhesions in patients with GER. However, in our group only one patient had pleural thickening and only one had pleural effusion. Lymphadenopathy was also not common in our patients.

Acute pneumonia was uncommon in our patients, as most CT studies were performed due to a decrease in lung ventilation (increased PCO_2 and/or decreased PO_2) and suspected increased chronic lung changes. Juvenile scoliosis in FD, which is well documented [2], can further compromise respiratory function. No obvious correlation was found between pulmonary parenchymal changes, pulmonary arterial enlargement, and the degree or side of scoliosis. Pulmonary arterial enlargements were present mostly in patients over the age of 20. Pulmonary hypertension can be attributed to restrictive lung disease due to scoliosis, high PCO_2, recurrent aspirations and subsequent fibrosis.

Esophageal dilation was found in 12 of our 34 patients. In 4 of these 12 patients there was no fundoplication at the time of the study. A dilated esophagus, filled with food/fluid, can cause apnea or overflow aspiration, especially when there is either fundoplication or lower esophageal stenosis below [18]. Compression of the esophagus between the aorta and the spine might cause esophagomegaly [19]. Such a mechanism could explain the esophageal dilation in only two of our patients. The dilation can probably be explained by abnormal innervations and peristalsis [20-22].

Silent fractures in FD patients as seen in three of the patients are most probably due to osteoporosis and to relative insensitivity to pain [23,24] Therefore, it is important to review CT examinations of FD patients with a bone window setting.

CONCLUSIONS

To the best of our knowledge this is the first study presenting characteristic chest CT findings in a relatively large series of FD patients, and the first attempt to relate these findings to underlying pathophysiological mechanisms characteristic of this disease. FD can serve as a model for lung disease caused by recurrent aspirations consistent with the CT characteristics of fibrosis, bronchial wall thickening, atelectases, and ground glass opacities. These changes are due to chronic airways and interstitial inflammation. Aggressive therapy of GER and associated aspiration are strongly recommended for these patients and other patients with a similar condition.

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