Review

Aspiration syndromes as a cause of bacterial colonization of the lower respiratory tract in children

Marios M. Papadopoulos[1], Kostas Douros[1], Michalis V. Anthracopoulos[2], Mark Everard[3], Kostas N. Priftis[1]

[1] 3rd Paediatric Clinic, University of Athens, "Attikon" Regional General Hospital, Athens, Greece
[2] Paediatric Pneumonological Unit, Paediatric Clinic, University of Patras, Rio Regional General Hospital, Patras, Greece
[3] Department of Respiratory Medicine, Sheffield Children's Hospital, Sheffield, UK

SUMMARY. Aspiration syndromes facilitate the colonization of the lower airways with bacterial pathogens and predispose to recurrent chest infections, chronic suppurative lung disease and bronchiectasis. In recent years important steps forward have been made in the understanding of the physiology of swallowing, the mechanisms underlying gastro-oesophageal reflux and the upper respiratory protective mechanisms for preventing aspiration. The diagnosis of aspiration however, and especially the establishment of a causal association with respiratory symptoms, remains challenging. Aspiration occurs sporadically and intermittently, and its manifestations are non-specific. There is no laboratory test that can establish with certainty whether or not aspiration lung disease is present; the diagnostic approach therefore remains primarily clinical, and laboratory investigations can only strengthen or weaken a clinical suspicion. *Pneumon 2011, 24(3):271-279.*

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Correspondence to:
Kostas N. Priftis
3rd Paediatric Clinic, University of Athens,
University General Hospital «Attikon»
1 Rimini street, 12462 Chaidari
Τηλ.: +30 210 5832228, Fax: +30 210 532229
e-mail: kpriftis@otenet.gr

INTRODUCTION

The term aspiration is used to describe the acute or chronic passage of food, gastric contents or saliva into the lower airways, with resulting acute or recurrent respiratory symptoms. These symptoms include chronic or recurrent cough, stridor, wheezing, recurrent infections, choking incidents, and ultimately, growth retardation.[1] Aspiration syndromes facilitate the colonization of the lower airways with bacterial pathogens and predispose to recurrent chest infections, chronic suppurative lung disease (CSLD) and bronchiectasis.[2]

In recent years, important steps forward have been made in the understanding of the physiology of swallowing, the mechanisms underlying gastro-oesophageal reflux (GOR) and the upper respiratory protective mechanisms for preventing aspiration. The diagnosis of aspiration however, and especially the establishment of a causal association with respiratory symptoms continues to be a challenge.

Aspiration occurs sporadically and intermittently, and its manifestations are non-specific, reducing the diagnostic validity of the information the medical history. In cases where there is coexistence with another pathological entity presenting with a similar clinical picture diagnosis may become even more difficult.[3] Classical examples of this are children with chronic lung disease of prematurity or tracheomalacia, the clinical presentation of which is chronic or recurrent cough, wheezing and atelectasis. These children may also have aspiration, which will complicate the interpretation of symptoms and the therapeutic approach.[4]

Micro-aspiration of regurgitated gastric contents or saliva during sleep can be observed in normal children, and there appears to be a threshold beyond which aspiration becomes clinically significant.[5] There is no laboratory test that can establish with certainty whether or not aspiration lung disease is present. The diagnostic approach, therefore, is primarily clinical, and laboratory investigation can only strengthen or weaken a clinical suspicion.[1]

TYPES OF ASPIRATION

Massive aspiration

Aspiration syndromes represent a spectrum of clinical entities. At one end of the spectrum is the massive aspiration of gastric contents, which presents with acute respiratory distress, while at the other end is chronic recurrent aspiration.[1,3]

The diagnosis of massive aspiration is usually clinical. The clinical presentation is severe, with cough, wheezing, respiratory distress, and sometimes fever. In the most severe cases, the disease can result in pulmonary oedema and acute respiratory insufficiency. The chest X-rays (CXR) show consolidation/atelectasis.

The symptoms are due mainly to injuries caused by the entry of acid material (pH <2.5) which damages the mucous membranes, alveoli and capillary network and promotes neutrophilic inflammation. Some, but not all, of the children with mass aspiration will develop secondary infection of the lower respiratory tract. This depends not only on the nature of the aspiration, but also on specific features of the particular host, such as inadequate mucociliary clearance, intubation, enteric feeding, antacid medications, etc.[1,6,7]

The first steps in coping with this emergency situation are support of the patient's vital signs and clearing of the airways. Bronchoscopy has an important role as a diagnostic and therapeutic tool. The use of surfactant mixed with normal saline during the bronchoalveolar lavage (BAL) procedure appears to improve the clinical course.[6-9] The choice of antibiotics depends largely on the age of the child, any previous use of antibiotics and comorbidities.

Chronic recurrent aspiration disease

The aspiration of small volumes into the lungs may occasionally be observed in healthy children, in the presence of a risk factor, such as an upper respiratory tract infection.[3] The main reasons for aspiration are malfunction of the swallowing mechanism, GOR and inadequacy of the protective mechanisms that normally prevent the passage of saliva through the glottis. Often, more than one of these factors may be present in the same child.

Recurrent small volume aspiration is aetiologically related with the development of CSLD, which, in some cases, may evolve into bronchiectasis.[2,10,11] Among the factors that predispose a child to recurrent aspiration are the following:[1]

1) Anatomical problems (micrognathia, cleft palate, tracheo-oesophageal fistula, vascular ring)[12]
2) Functional disturbances (achalasia, GOR, tumours, scleroderma)
3) Mechanical causes (rhino-gastric or endotracheal tubes, tracheostomy)
4) Neurological immaturity or disease (prematurity, anaesthesia, convulsions, cerebral palsy, vocal cord paralysis, muscular dystrophy).

Aspiration due to dysfunction of the swallowing mechanism

Swallowing is a complex process which, in order to be completed, requires voluntary and involuntary cooperation and synchronization of various different anatomical structures such as the oral cavity, pharynx, larynx, and oesophagus. This mechanism matures after birth and during the first years of life, following a path parallel to the maturation of the central nervous system (CNS). Aspiration problems occur more frequently in children with neurological problems,[1,13-15] but they can also occur in "healthy" children, especially those born prematurely or suffering from acute bronchiolitis.[16]

Aspiration in GOR

The occurrence of GOR in children with recurrent respiratory symptoms is well documented, but an aetio-

logical relationship is difficult to establish.[17-19] In a few studies of children with suspected pulmonary aspiration, simultaneous tracheal and oesophageal pH monitoring confirmed the presence of gastric contents in the lower airways.[20,21] It has been suggested that GOR in the absence of swallowing malfunction is less likely to cause lung infection[21] and that chronic irritation of the larynx from the acidic gastric contents may adversely affect the reflex protective mechanism, thereby increasing further the risk of aspiration.[22]

Saliva aspiration

The diagnosis of recurrent saliva aspiration is difficult and frequently it is established with significant delay and only after lung damage has occurred. Children with neurological diseases usually aspirate saliva. The aspiration appears to be due to immaturity of the swallowing mechanism and malfunction of the laryngeal reflexes, and not to the increased production of saliva. In general, there should be a high level of suspicion in children with excessive salivation, choking from secretions, major neurological problems, cleft palate, median line anomalies, and syndromes such as CHARGE and Moebius. These children should be investigated as soon as possible.[1,3,12]

Pathophysiology

The pathophysiological mechanisms that explain the colonization of the lower airways with micro-organisms depend mainly on the nature (food, gastric contents, saliva) and chemical characteristics (acidic, non-acidic) of the aspirated material and whether the aspiration is acute or chronic.

The colonization of the lower airways results from transfer with the aspirated material of bacteria of the normal flora of the rhinopharynx and oral cavity. When antacid medications are used the altered gastric pH favours the colonization of the gastric mucosa with micro-organisms which, in the event of aspiration of the gastric contents, will be transferred to lower airways.[1,3]

When the micro-organisms settle in the bronchi they promote local endobronchial inflammation, usually without noticeable symptoms, attracting neutrophils and increasing the expression of inflammatory mediators such as IL-8.[23,24]

Recurrent aspiration will finally lead to chronic inflammation which is accompanied by changes in the number and type of secretory cells and an increase in the quantity and viscosity of mucus. These changes in the mucus adversely affect the effectiveness of mucociliary clearance, which may also be impaired by the presence of micro-atelectases, and the chemical irritation caused by the aspirated material.[1,3,22,23]

Chronic inflammation leads to secondary tracheal/bronchial wall malacia which is accompanied by changes in the bronchial secretions that facilitate bronchial inflammation, colonization of airways with bacteria and evolution of chronic infection.[1,25]

Recurrent aspiration results in a vicious cycle, with chronic inflammation inducing infection and vice versa. Chronic inflammation impairs the defence mechanisms of the respiratory tract and facilitates the retention of micro-organisms in the bronchial mucosa,[2,3,26] resulting in the development of CSLD. The causative association of recurrent aspiration with CSLD and bronchiectasis has been reinforced by the finding of the same bacteria (non-typable strains of *H. influenzae, M. catarrhalis* and *Pneumonococcus*) in the rhinopharynx and the lower respiratory tract of children with bronchiectasis.[27] These micro-organisms multiply at a slow pace, mainly in the bronchi, producing biofilms. Their multiplication is accelerated during exacerbations, when the infection extends into the breathing zone, with the development of alveolar damage and pneumonia.[28]

The clinical picture

The respiratory manifestations of chronic recurrent aspiration depend on the age of the child, the characteristics (liquids, creams, saliva, gastric fluid) and quantity of the aspirated material, and the presence or not of neurological problems.[1,3,29] Recurrent or persistent symptomatology from the lower respiratory tract in children suffering from neuromuscular diseases increases the likelihood of aspiration disease. Healthy immunocompetent infants may be prone to suffer from aspiration due to congenital anomalies, such as tracheo-esophageal fistulas and clefts, or immaturity of the swallowing mechanism.

Recurrent or chronic wet cough[30] is the most characteristic symptom of children with recurrent aspiration. Sometimes, when the cough is due only to chemical irritation of the mucous membranes or the activation of reflex mechanisms, it may sound dry. Cough is sometimes absent in children below one year of age and in children with neurological diseases (silent aspiration due to abolition of the cough reflex). Apart from cough, other symptoms which are rather common, especially in infants, include noisy breathing (rattles, stridor, wheezing), and episodes

of choking or apnoea (desaturation episodes with cyanosis). There is also a probable relationship between GOR and chronic nasal symptoms or chronic otitis media with effusion.[1,3,29,31,32] Risk factors such as dysmorphic features (micrognathia) and anatomical defects (clefts) should be identified, and it may be necessary to monitor closely such children during feeding.

The diagnostic approach

Although the causal association of chronic recurrent aspiration with CSLD has been well documented it is usually difficult to diagnose aspiration as the cause of respiratory symptoms.[2,26,28]

The documentation and monitoring of endobronchial infections is usually performed by sputum culture. The easiest way is to take a sample on spontaneous coughing, but this is rarely possible in children. Alternative methods are the use of cough swabs (after intense respiratory physiotherapy), and sampling of induced sputum (after inhalation of hypertonic solution), but bronchoscopy with BAL is considered to be the most reliable. After endobronchial infection has been documented, the next and most challenging step is to confirm that aspiration is the responsible aetiological factor.[2,26,32]

If there is suspicion of chronic bronchitis due to recurrent aspiration, it is essential to assess the lungs radiologically with CXR and high definition computed tomography (HRCT). CXR may show thickening of the bronchial walls, hyperinflation, and plate atelectases. A characteristic, although not pathognomonic, finding is the localization of lesions in the basal and superior segments of the lower lobe and the posterior upper lobe. Although CXR is a valuable scanning tool, the gold standard of the radiological assessment of chronic purulent bronchitis is the HRCT scan, since it can provide detailed information about the central and especially the peripheral airways and the lung parenchyma. Bronchial thickening, bronchiectasis, air trapping, ground-glass opacities and centrilobular opacities ("tree-in-bud") constitute the most common, although not specific, findings of aspiration.[1,2,33]

Published diagnostic algorithms are more interesting in terms of training than in clinical practice.[3]

Swallowing dysfunction

Videofluoroscopy can monitor the bolus from its formation to its passage into the pharynx and oesophagus. It can identify problems with the swallowing mechanism, such as secretions or food remnants left in the supraglottic area, and occasionally aspiration during swallowing.[34] Although it is a valuable diagnostic tool to complement clinical evaluation, it has the drawback of being a relatively labour-intensive form of assessment, and it involves ionizing radiation. While a positive result is highly specific, a negative result does not exclude aspiration, and inter-subject variation in interpretation is a potential problem.[3,35]

Fiberoptic endoscopic evaluation of swallowing is an invasive method, but it has the advantage of not exposing the patient to radiation. It provides important information on the anatomy of the region and can be used to evaluate children who are not fed by mouth. It assesses the adequacy of the protective mechanisms against aspiration and evaluates the oral and pharyngeal phase of swallowing, but it cannot give information about the events following the contraction of pharynx.[36-38]

These two methods provide different information and sometimes need to be interpreted in combination.

A large number of lipid laden macrophages (LLM) in the BAL (Oil-O-Red stain positive) have been considered as a strong evidence of aspiration. In many studies the alveolar LLM index has been used. To calculate this index the amount of fat contained in 100 macrophages is assessed, giving to each macrophage a grade of from 1 to 4. Macrophages with no visible lipid staining of the cytoplasm are scored "0", while grades 1, 2, 3, and 4 represent those cells with 25%, 25%-50%, 50%-75%, and >75% of their cytoplasm opacified by lipid, respectively. The index ranges from 0-400.[24] A wide range of cut-off points have been used to diagnose aspiration, ranging from 67 to 200. It is now recognized, however, that elevated levels of LLM can be seen in pulmonary diseases with no evidence of aspiration and, on the other hand, 'normal levels' can be observed in children known to have aspiration.[39,40] It is probable that raised LLM levels may be due also to inflammation from other causes, such as CSLD, with the lipid membrane of necrotic inflammatory cells being taken up by macrophages, while levels could be low in older children in whom fluids are generally in the form of water or juice, rather than milk.[1,3,40-42]

In infants with swallowing dysfunction which may be due to neurological disease, if the initial results are negative, diagnostic evaluation must be extended to include, for example, brain MRI, EEG, preliminary evaluation for metabolic diseases, and possibly more detailed tests to cover the possibility of diagnosis of underlying evolutionary neurological disease.[1,3]

Aspiration due to GOR

The 24 hour oesophageal pH study is considered the gold standard for quantifying acid reflux, but it holds the potential for technical difficulties and non-acid reflux will not be detected. These limitations can reduce the sensitivity of the method.

Multichannel intraluminal impedance monitoring measures reflux from the retrograde passage of a liquid bolus from the stomach through the oesophagus. It is pH independent and so can detect non-acid reflux.[43-45] Simultaneous measurement of the pH allows the characterization of the reflux wave as acidic or non-acidic. This method showed that non-acid reflux is common in infancy and that the aspiration of non-acidic material causes significant respiratory problems.[46,47]

Kawamura *et al* examined the relationship between reflux and persistent respiratory symptoms in a group of infants with frequent regurgitation, and observed that 85.7% of reflux incidents recorded with intraluminal impedance monitoring, were associated with abnormal sleep and 73% of them reached hypopharynx. Only 11.8% of the recorded events were acidic.[48] The major limitation of intraluminal impedance testing is the absence of normal values for children.

The presence of LLM in the BAL cannot establish a causal relationship between GOR and aspiration.[49-51] Moran et al. examined intubated infants on mechanical ventilation who were receiving enteral nutrition with lactose containing solutions. The infants who were found to have lactose in the trachea also had markedly elevated LLM in the BAL.[52] The simultaneous use of intraluminal impedance monitoring, oesophageal pH study and measurement of LLM in BAL might be a required combination for demonstration of a causal relationship between GOR and chronic aspiration into the lungs.

Determination of pepsin (a protease produced by pepsinogonen under conditions of an acidic pH) in the BAL is a reliable marker of aspiration of gastric contents.[53-55] This method has not been taken up widely due to the lack of a commercially available assay (although this deficiency appears likely to be overcome).

The detection of bile acids in the BAL, especially if combined with increased expression of growth factor TGFβ-1 and increased fibroblast proliferation (risk of pulmonary fibrosis), may prove to be useful indicators of gastric aspiration in the future.[53]

Exhaled breath condensate (EBC) was first described in 1980 and is an evolving method for the non-invasive assessment of airway inflammation.[56-59] The patient breathes quietly in a cooled cylinder for about 10 minutes; the condensate is then collected and analyzed for numerous biomarkers (nitric oxide, 8-isoprostane, hydrogen peroxide, total nitrogen oxides, pH, cysteinyl leukotriene, total protein, etc.). Molecular markers of GOR aspiration, such as pepsin or bile salts can also be measured in EBC. Unfortunately, the method is not currently available outside the research setting. Although there continues to be much controversy regarding EBC, especially in its comparison with BAL,[60,61] its non-invasive character makes it a potentially valuable tool in the study of GOR aspiration and its consequences on the lungs.

Radionuclide scintigraphy with Technetium-99m sulfur colloid given with milk (milk scan) can detect aspirated material in the lung after a meal. However, the method has low sensitivity and cannot differentiate between aspiration of milk during swallowing and later aspiration of gastric contents.[62,63] A study with simultaneous pH monitoring, underlined the limitations of the method, showing that a significant proportion of the positive milk scans were accompanied by normal pH-metry.[65]

Barium swallow is an imaging modality capable of demonstrating anatomical abnormalities, such as fistulas or vascular rings, and it gives information about the mobility of the oesophagus. The method has low sensitivity, which can be explained by the intermittent nature of recurrent aspiration.[62-64]

Recurrent aspiration of saliva

Children with chronic endobronchial infection should be investigated for recurrent aspiration of saliva, if there is a suggestive history and no response to interruption of feeding by mouth or antireflux therapy. The presence of salivation, choking from secretions, neurological problems, clefts, vocal cord paralysis, congenital obstruction of the upper respiratory tract, syndromes such as CHARGE or Moebius, all increase the likelihood of recurrent aspiration of oral secretions.[1,3]

A standard method for investigations is saliva scintigraphy, which is performed by placing radioactive material in the oral cavity, but its sensitivity varies.[66] Very useful is the flexible endoscopic evaluation of swallowing (FEES), especially combined with sensory testing of larynx. The latter is performed by applying a calibrated puff of air to the aryepiglottic fold region of the larynx, with stimulation inducing an involuntary reflex. A positive laryngopharyngeal sensory stimulation test is associated with laryngeal penetration and aspiration, pooled hypopharyngeal secretions, and a history of pneumonia,

neurological disorders, and GOR.[67,68]

An alternative method of testing for chronic recurrent aspiration in children with tracheostomy is the placement of an inert dye in the oral cavity and its detection in the tracheostomy secretions. It would not be prudent, however, to attribute recurrent respiratory infections solely to aspiration, since in these children many other risk factors may be involved.[69]

"Difficult" cases

There are children who have a history suggestive of recurrent aspiration, compatible radiographic findings, and increased numbers of LLM in the BAL, but nevertheless have multiple instances of negative evaluation for swallowing dysfunction or GOR. In these "difficult" cases the diagnosis of chronic aspiration due to incoordinated swallowing is established by "clinical trial" through the implementation of nasogastric tube feeding and the cessation of feeding by mouth, which would be expected to result in improvement of the respiratory symptoms.[3]

Treatment options

The treatment of children with recurrent aspiration is aimed at improving the process of oral feeding in order to ensure the necessary hydration and caloric intake, and at the same time, reduce the aspiration of oral and stomach contents.[1,3]

The impairment of the swallowing process is a complex problem that requires treatment by an experienced team of paediatric pulmonologists, paediatricians, gastroenterologists, ENT specialists, speech therapists, possibly paediatric surgeons, and specialized nurses. Education of the parents and changes in feeding conditions (posture, density of food) are often very helpful.[70]

Gastrostomy, duodenostomy

Gastrostomy or duodenostomy and application of feeding through a catheter, is applied in cases where feeding by mouth is insufficient to meet the children's nutritional needs. It is also indicated in cases where improvement of the feeding process is insufficient to control the respiratory symptoms. In children with neurological diseases and aspiration, it is essential to consider surgery for treatment of GOR, along with feeding through gastrostomy.[71,72] Cricopharyngeal myotomy must be decided early in cases of aspiration due to cricopharyngeal achalasia.[73]

Children with GOR

The treatment of CSLD in children with GOR presents many problems.[60] In mild cases the use of thickening agents in the milk and feeding with solid foods may reduce the frequency and amount of non-acidic reflux. H2-receptor blockers and proton pump inhibitors are effective drugs for the treatment of oesophagitis, but are insufficient in reducing recurrent aspiration and the ensuing chronic inflammation in the respiratory tract. This may partly be explained by the significant percentage of non-acidic reflux observed in children.[1,3,74,75]

Surgical treatment

The most common surgical treatment is the Nissen fundoplication which involves wrapping the upper part of the stomach around the oesophagus. It is considered an absolute indication in children with severe or persistent respiratory symptoms (recurrent pneumonia) and GOR.[72] Remission of symptoms is observed in a significant proportion of children (48 - 92%), but unfortunately, the rates of relapse or failure are high, especially in children with underlying neurological disease (up to 27%). A major complication seen postoperatively is the accumulation of secretions in the oesophagus, which may result in lung aspiration. This complication is more prominent when there is a concurrent impaired mobility of the stomach, in which pyloromyotomy is indicated.[76,77]

Anticholinergic medication

Persistent or recurrent respiratory symptoms due to aspiration of saliva in children with neurological disorders have been treated with oral administration of anticholinergic preparations. The limitations of this therapeutic approach are the short duration of the beneficial effect, and the considerable side effects that are observed. Furthermore, there have been no controlled studies on their effectiveness in preventing aspiration.[78]

Inactivated botulinum neurotoxin

The application of inactivated *botulinum* neurotoxin in the submandibular glands, with or without scopolamine, has been suggested as an alternative method. No major side effects have been observed, but it is still not known whether this method improves respiratory symptoms.[79,80]

Submandibular and parotid gland removal

The removal of the submandibular and parotid glands with preservation of minor salivary glands appears to satisfactorily control excessive salivation, and at the same time decrease respiratory infections.[81]

Tracheostomy

Tracheostomy affects the mobility of the larynx and facilitates saliva aspiration. Surgical separation of the larynx and trachea is usually an irreversible process with major post-operative implications.[82-84]

CONCLUDING REMARKS

Chronic wet cough and chronic endobronchial infection cannot be easily ascribed to recurrent aspiration. The ultrasound scan of the glottis area is a promising method for evaluating swallowing disorders.[85] Evaluation of pepsin in the BAL is a possible marker of aspiration. Animal studies have revealed a series of inflammatory mediators that could be used as markers of aspiration. It appears that a varying combination of inflammatory mediators can be used, depending on the origin and composition of aspirated material.[24] In addition, preliminary results suggest that the use of polystyrene microspheres phagocytosed by alveolar macrophages could be used as a very specific marker for the diagnosis of aspiration.[86]

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