Definition, incidence and etiology: what's new in the 21st century?

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Actually, achalasia can be defined as a primary esophageal motor disorder characterized by esophageal aperistalsis and abnormal post-deglutitive lower esophageal sphincter (LES) relaxation. Its incidence varies from 0.03 to 1.63 cases per 100,000 people per year and increases with age, while the prevalence is almost 10/100,000 with no difference between the sexes. Regarding etiology, the most frequent histologic alteration is represented by the loss of the myenteric nerve fibers regulating inhibitory nitrergic neurotransmission in the LES, with the presence of a lymphocytic infiltrate and collagen deposition. The cause of this loss remains unclear. Among the theories proposed, the infectious, hereditary and autoimmune etiologies have been widely investigated. The only infectious agent identified as a cause of achalasia is Trypanosoma Cruzi, responsible of Chagas' disease. Regarding hereditary component, in rare cases achalasia presents as part of a genetic syndrome such as Down syndrome, Allgrove syndrome and familial visceral neuropathy. Although, no disease-specific gene has been identified. The autoimmune hypothesis has focused on the association of specific HLA classes with achalasia. However, no consistent association has been observed across studies.
Despite increasing understanding of the physiopathology of achalasia, its etiology remains largely unknown. The onset of the disease is characterized by chronic inflammation of the myenteric plexus of the esophagus secondary to an environmental insult. Probably, genetic factors are involved in the development of achalasia, although the precise molecular basis of the disease has not been identified.

KEY WORDS: Achalasia, Epidemiology, Etiology

Introduction

The first description of achalasia is attributed to an English physician, Willis, in 1674, who described a man from Oxford in otherwise good health who vomited 'whatsoever he had eaten'. Willis treated this 38-year-old patient with a whale bone rod with a small piece of sponge on its end inserted into the esophagus to relieve the obstruction. He suggested that the disease could be due to the loss of normal inhibition in the distal esophagus[1]. Further cases of similar description are found through the next two centuries using names such as cardiospasm, aperistalsis, megaesophagus, esophageal dystonia, simple ectasia of the esophagus, and dolichoesophagus[2]. The name achalasia did not come into use until the twentieth century when published as 'achalasia of the cardia' by Hurst[3]. The term achalasia comes from Greek for failure to relax, implicating failure of lower esophageal sphincter (LES) relaxation as a cause of the clinical manifestations of this disease. Actually, it can be defined as a primary esophageal motor disorder characterized by esophageal aperistalsis and abnormal post-deglutitive LES relaxation[4,5].

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Epidemiology

Despite its being recognized more than three centuries ago, limited information is available regarding the epidemiology of achalasia worldwide. Due to the rarity of the disease, prospective epidemiologic studies are difficult to conduct. The available epidemiologic studies are mostly retrospective and based on hospital records from local areas in a few countries. The true incidence of achalasia could might therefore be either over or underestimated. However, from an extensive review of the literature, actually it varies among the studies from 0.03 to 1.63 cases per 100.000 people per year, while the prevalence appears to be almost 10/100.000. In all studies it was relieved a progressive increase in prevalence as it reflects the low mortality from achalasia. The disease has an equal sex diffusion and may emerge at any age, although the incidence increases with age and peaks in the seventh decade. Additionally, a small incidence peak occurs in the 20-40 years age group. In Table I we report the results of the published epidemiological studies.

Etiology and Pathophysiology

A hallmark of achalasia is failure of complete LES relaxation, which is a complex mechanism requiring the coordinated interaction of nerves, smooth muscle, interstitial cells of Cajal (ICC) and hormones. At rest the LES is tonically contracted. Initiation of a peristaltic wave in the esophagus is accompanied by a decrease in LES pressure as a result of smooth muscle relaxation. LES relaxation occurs when the mechanisms that lead to tonic contraction are interrupted. Relaxation is predominantly neuronally initiated, coordinated by both spinal and vagal afferents. Vagal efferent cell bodies lie in the dorsal motor nucleus of the vagus. The processes that originate from the cell bodies of vagal efferents in the caudal region of the vagus dorsal motor nucleus innervate inhibitory neurons that lie in the LES myenteric plexus through cholinergic nicotinic neurotransmission[20]. Terminals of the vagal efferents not only lie in close proximity to the inhibitory myenteric plexus neurons, but also end close to a specialized cell type known as the ICC within the LES[21]. These specialized cells have multiple functions[22] including amplification of neuronal signals. It appears that more than one neurotransmitter mediates neurotransmission between the inhibitory myenteric neuron and ICC and smooth muscle. The predominant inhibitory neurotransmitter is nitric oxide (NO), and inhibitory neurotransmission has been demonstrated to be the dominant pathway for LES relaxation[23,24]. However, the mechanism that results in NO-induced LES relaxation at the single cell level is not yet fully understood and also the role of ICC in mediating enteric neurotransmission is not well elucidated.

The complex physiology of LES relaxation highlights the multiple potential pathological defects that could give rise to the clinical picture of achalasia. Potential targets include extrinsic and intrinsic innervations, ICC and smooth muscle. Among the most consistent described abnormalities, there is the loss of myenteric nerve fibers in the LES and esophageal body, already documented six decades ago. In patients with long standing achalasia, myenteric ganglion cell bodies are markedly diminished or absent. Recently, immunohistochemical techniques have demonstrated the presence of a lymphocytic infiltrate and collagen deposition within the myenteric plexus. The majority of lymphocytes present in mild or clinically early achalasia are T-lymphocytes. These find-

Table I - *Published studies of incidence and prevalence of achalasia*

Study population	N. pts	Period	Incidence (cases/100,000/year)	Prevalence (cases/100,000/year)
Rochester[6]	11	1935-1964	0.6	
Virginia[7]	31	1975-1978	0.6	
Scotland[8]	699	1974-1983	1.1/1.2 (a)	11.2
Oxford[8]	216	1974-1983	0.9/0.9 (a)	9.99
Cardiff[9]	48	1926-1977	0.4	
Nottingham[10]	53	1966-1983	0.5	8
Edinburgh[11]	25	1986-1991	0.8	
Israel[12]	162	1973-1978	0.8	7.9-12.6
New Zealand[13]	152	1980-1984	1.0	
Zimbabwe[14]	25	1974-1983	0.03	
Singapore[15]	49	1989-1996	0.3	1.8
Iceland[16]	62	1952-2002	0.55	8.7
Leicester[17]	14	1986-2005	0.89	
Alberta[18]	463	1995-2008	1.63	10.82
Veneto[19]	365	2001-2005	1.59	

a: male/female

ings suggest an immune-mediated destruction of myenteric neurons. There is little evidence to suggest a defect in smooth muscle, but together with the loss of myenteric neurons, the lack of ICC has also been reported[25,26] and this has been further substantiated by electron microscopy[27]. The central role that loss of nitrergic neurons plays in the pathophysiology of achalasia is highlighted by studies on animals[28] and on humans; Mearin et al. investigated NO synthase activity in gastroesophageal junction specimens from patients with achalasia and non-achalasic controls who underwent oesophagectomy for cancer. There was a complete loss of nitrergic neurons in all achalasic specimens. In contrast, NO synthase activity was detected in each of the samples obtained from control samples[29]. Numerous subsequent studies have confirmed the substantial decrease or complete lack of NO synthase-positive innervation in the LES myenteric plexus as well as in the gastric fundus of the achalasic patients[30,31].

Although general consensus now exists that the non-relaxing LES and aperistaltic esophageal body result from the loss of inhibitory nitrergic neurotransmission, often accompanied or preceded by an inflammatory infiltrate; the cause remains not elucidated. Among the numerous theories proposed to explain the development of achalasia, the infectious, hereditary and autoimmune etiologies have been most widely investigated.

Regarding the infectious etiology, it is now clear that infective agents can cause achalasia symptoms. A defined secondary achalasic syndrome occurs in Chagas' disease resulting from infection with the parasite Trypanosoma Cruzi. It currently affects almost 12 million persons, mainly in Latin America[32]. Parasites are usually transmitted by a hematophagous species of triatomine bug of the Reduviidae family. The progression of infection depends on the initial inoculum, on the genetic diversity of Tripanosoma Cruzi and on the host immune response. The chronic phase appears 2-4 months after infection and, initially, no symptoms are observed: this latency may last throughout life. Up to 30% of infected people may develop clinical forms of the disease with cardiac or digestive involvement, usually 10-15 years after infection[33]. Involvement of digestive organs is mainly attributed to neuronal damage induced by immune and inflammatory processes elicited by Tripanosoma Cruzi[34].

Other viral infections have been investigated as possible causes of achalasia, given the lymphocytic nature of the inflammatory infiltrate observed in the achalasic specimens. The epidemiologic data in this regard have been inconsistent. Initial case-control studies showed high measles antibody titers in achalasic patients compared to healthy controls, but no difference in Varicella Zoster virus (VZV), Herpes simplex virus-1 (HSV-1) and other viral antibody titers. Subsequent studies have shown elevated VZV titers compared to controls and evidence of viral VZV DNA in the esophagus in several of the achalasic patients[35]. However, PCR in the achalasic specimens failed to demonstrate viral products in the esophageal tissue[36]. In none of the studies a causal link has been established; thus the infectious etiology of achalasia remains an unclear matter.

Regarding the hereditary component in the etiology of the disease, achalasia rarely presents as a part of a genetic syndrome such as Down syndrome (DS), Allgrove syndrome, familial visceral neuropathy (FVN) and achalasia microcephaly syndrome.

Achalasia occurs in approximately 2% of DS cases, which far exceeds the prevalence of around 0.01% observed in the general population (200-fold increased risk)[37]. The gastrointestinal abnormalities observed in DS are also apparent on the histological level. Research has demonstrated a reduction in the number of neurons in the esophageal plexus ganglia; however, chromosome 21 contains approximately 425 genes and it is unclear which of them contribute to the development of achalasia as a result of trisomy.

The Allgrove (triple A) syndrome is an autosomal recessive disorder characterized by the triad of achalasia, alacrima and ACTH-resistant adrenal insufficiency. The syndrome is caused by homozygous or compound heterozygous mutations in the AAAS gene on chromosome 12q13 which encodes for the ALADIN (alacrima-achalasia-adrenal insufficiency-neurologic disorders) protein. Achalasia occurs in almost 75% of patients with Allgrove syndrome and it is usually diagnosed in infancy. Post-mortem studies of patients with this syndrome have reported the absence of ganglion cells and nerve fibers in the lower esophagus[38]. The precise function of ALADIN is unknown. However, the fact that AAAS gene is expressed in both neuroendocrine and cerebral structures suggest that the protein plays a role in the development of the peripheral and central nervous systems[39].

FVN is a rare disorder that is caused by abnormalities of the intestinal myenteric plexus. Clinical presentation is variable and includes achalasia, gastroesophageal reflux, intestinal dismotility, dysarthria and peripheral neuropathy. Only eight families with FVN have been reported in literature; however, the molecular basis of the syndrome remains speculative since no specific gene has yet been identified.

In a small number of families, achalasia is associated with microcephaly and mental retardation, a constellation defined as the achalasia microcephaly syndrome. It is likely that this syndrome has an autosomal recessive mode of inheritance, but no disease-causing gene has been identified.

Regarding autoimmune etiology, most attention has been focused on the association of specific HLA classes with achalasia. The HLA class II molecules are associated with several autoimmune diseases, and research findings suggest that disturbances in the autoimmune response also play a crucial role in achalasia: T-lymphocytes that are able to recognize certain HLA class

II antigens are the predominant cell type in infiltrates of the esophageal myenteric plexus in achalasic specimens[40]. Furthermore, other researches have demonstrated a higher prevalence of antimyenteric autoantibodies in achalasic patients with certain HLA class II antigens[41,42].

The HLA class II locus is located on chromosome 6p21 and contains more than 30 genes including the major class II genes HLA-DP, HLA-DQ and HLA-DR. Most of the studies performed to test whether certain HLA polymorphisms increase the risk for achalasia have focused on HLA-DQ, and some have found an association between achalasia and various alleles (HLA-DQw1, HLA-DQA1*0101, DQB1*0502, DQB1*0601 and DQB1*0602). However, no consistent association has been observed across studies[41-45]. Various HLA-DR variants have been tested for association with achalasia although these associations were even weaker than those reported for HLA-DQ[41,43-45].

A further achalasia candidate gene selected on the basis of its involvement in autoimmunity is the protein tyrosine phosphatase N22 gene (PTPN22) on chromosome 1p13. PTPN22 encodes a lymphoid-specific phosphatase (LYP) which down-regulates T-cell activation. It has been postulated that the PTPN22-allele 1858T promotes an autoimmune response which results in chronic inflammation[46]. A gender-specific association has been observed between this variant and achalasia: the T allele of C1858T showed a significant association in female patients compared to controls[47].

A recent research has identified one further achalasia candidate gene that may be involved in the inflammatory processes. The Rassf1a-knockout mouse has been proposed as a model of human achalasia. These mice are more susceptible to the development of a megaesophagus (20 vs 2%), which has similar histopathological features to those of human achalasia, e.g. a loss of neurons in the esophageal myenteric plexus[48]. The Ras association domain family member 1 gene (RASSF1) is located on chromosome 3p21. The observation of a chronic inflammatory infiltrate of the myenteric plexus and the muscle layers and the fact that other members of the RASSF-family regulate immune reactions have led to the hypothesis that RASSF1 may influence the inflammatory processes[48].

Other researches have focused on the genes involved in inhibitory neurotransmission within the esophageal myenteric plexus, i.d. the genes involved in the neurotransmission of NO and vasoactive intestinal peptide (VIP)[49]. However, no clear association has been demonstrated from these studies.

Conclusion

Despite increasing understanding of the pathophysiology of achalasia, its etiology remains largely unknown. It is now widely accepted that the onset of the disease is characterized by chronic inflammation of the myenteric plexus within the esophagus subsequent to an environmental damage. However, the external and internal factors that initiate and modulate the inflammation, which ultimately destroy the cells of the myenteric plexus, still await identification. There are several reasons for assuming that genetic factors are involved in the development of achalasia; although, the precise molecular basis of the isolated forms of achalasia, which represent the majority of patients, has not yet been identified. Given the severity of this disease, an improved understanding of its primary causes is mandatory. Modern molecular techniques have led to the identification of the responsible genetic factors for a host of diseases. There is hope that such studies will also help us to clarify the biology of achalasia, so facilitating early diagnosis and therapeutic strategies.

Riassunto

Attualmente, l'acalasia può essere definita come un disordine motorio esofageo caratterizzato da assenza di peristalsi del corpo esofageo e mancato rilasciamento dello sfintere esofageo inferiore (LES) in risposta alla deglutizione. La sua incidenza varia da 0.03 a 1.63 nuovi casi per 100.000 abitanti per anno, mentre la prevalenza è circa 10/100.000, con nessuna differenza tra i sessi ed incidenza crescente con l'età. Riguardo l'etiologia, la più frequente alterazione istologica è rappresentata dalla perdita delle fibre nervose del plesso mienterico che regolano la neurotrasmissione inibitoria a livello del LES, con la presenza di un infiltrato linfocitario e la deposizione di collageno a tale livello. La causa di tale perdita resta non chiarita. Tra le teorie proposte, quella infettiva, ereditaria ed autoimmune sono state ampiamente oggetto di studio. L'unico agente infettivo riconosciuto causa dell'acalasia è il Tripanosoma Cruzi, responsabile del morbo di Chagas. Riguardo la componente ereditaria, in rari casi l'acalasia si presenta come parte di una sindrome genetica come la sindrome di Down, la sindrome di Allgrove e la neuropatia viscerale familiare. Tuttavia, nessun gene specifico della malattia è stato identificato. L'ipotesi autoimmune è stata focalizzata sull'associazione di specifiche classi HLA con l'acalasia. Comunque, nessuna associazione significativa è stata osservata nei vari studi.

Nonostante il progressivo incremento della comprensione della fisiopatologia dell'acalasia, la sua etiologia resta largamente sconosciuta. L'insorgenza della malattia è caratterizzata dall'infiammazione cronica del plesso mienterico dell'esofago secondaria ad un insulto ambientale. Probabilmente, fattori genetici sono coinvolti nell'insor-genza dell'acalasia: tuttavia la base molecolare precisa della malattia non è stata identificata.

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