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Review Article

Does Young's syndrome exist?

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Abstract

Background and methods: Young's syndrome describes a combination of male infertility, azoospermia, bronchiectasis and sinusitis. Although Young's syndrome is a well accepted disorder within the realms of infertility medicine, it is also accepted as being a potential cause of sino-nasal disease which is rarely seen by otolaryngologists. However, the significance of the sinus component within this triad is not fully understood. To gain further insight into the relationship of sinusitis with Young's syndrome, we reviewed all of the currently available published literature.

Results: Within the reviewed literature, the diagnosis of sinusitis in Young's syndrome was crude and poorly defined; there was little emphasis on sinus disease in most publications.

Conclusions: The prevalence of Young's syndrome is reported to be declining, and the level of evidence regarding sinus disease within this syndrome is limited to case series only. There is, in fact, little evidence to support Young's syndrome being a significant aetiological factor for sinus disease, nor indeed to support the existence of Young's syndrome as an entity in its own right. The only documented aetiological factor is mercury exposure in childhood, an event that is seldom currently encountered; this would support our theory of the extinction of the condition. As an incidental finding, we found that the term Young's syndrome refers to two different medical conditions.

Key words: Sinusitis; Bronchiectasis; Infertility; Aetiology; Prevalence

Introduction and background

Young's syndrome is a rare disease comprising three components: obstructive azoospermia, bronchiectasis and sinus disease. It is a recognised cause of male infertility and is a well known and accepted diagnosis in the field of infertility. The exact nature and natural history of the sinus disease component is not widely understood.

The aim of this review article was to formulate a current, comprehensive account of the sinus disease component of Young's syndrome. The review will focus on the genetics, aetiology, clinical findings and differential diagnosis of Young's syndrome.

Methods

A literature search was undertaken using limits set to English and humans. The search parameter 'Young's syndrome' identified 42 articles; 37 were relevant and seven were review articles. The articles rejected had the following search terms: 'Young's modulus' (two), 'Young's valve' (one) and 'Young's operation' (two). An additional search strategy was undertaken to include books, the internet, theses, libraries, e-mail lists, academic subject gateways, reports and 'grey literature', reviews, and citation indexes. This search yielded one further article which was deemed to be relevant. A total of 38 articles were reviewed.

History of Young's syndrome

In 1970, David Young, a Liverpool urologist, observed that 54 per cent of patients with obstructive azoospermia also had evidence of lung defects.[1] He called the association between azoospermia and pulmonary disease the Berry–Perkins–Young syndrome. The syndrome was shortened to Young's syndrome by Hendry in 1978,[2] and was described as a triad of obstructive azoospermia, sinusitis, and bronchitis or bronchiectasis.

However, the term Young's syndrome had been used previously, in 1953, to describe a condition in women associated with prolonged fetal growth, high fetal or neonatal mortality, large babies, hyperlactation, obesity and diabetes.[3] Only two case reports were described. The syndrome received no further mention in the literature and has now been disregarded.

Aetiology

The prevalence of Young's syndrome is unknown. In the 1980s, the syndrome was reported to affect one in

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500 males[4] and was described as being commoner than cystic fibrosis (CF).[5] More recently, only a handful of case reports have been published on this syndrome.[6–8] A reduction in the use of mercury in Europe and the USA has been cited as a potential reason for this decline. Mercury exposure in childhood is likely to be the only aetiological factor identifiable in Young's syndrome. A history of mercury intoxication (Pink's disease) was seen in 10 per cent of Young's syndrome patients in one series.[9] Mercury inhibits enzymes containing sulphydryl by reacting with thiols to form mercaptides. Mercaptides are thought to inhibit glycolysis, which is necessary for the normal function and energy supply of sperm and cilia.[10]

Young's syndrome is rare in the USA, where mercury usage was discouraged by the Food and Drug Administration in 1933.[11] In the UK, mercury-containing calomel was removed from teething powders and worm medications in 1955. It was still used in the UK and Australia (which shares similar prevalences with the UK) until 1966, and it was still reported to be used in ethnic remedies[12] and skin lighteners as recently as 1993.[13] This reduction in mercury exposure was the reason given for Hendry and colleagues' observation that the prevalence of Young's syndrome has greatly declined in recent times – from 114 (50 per cent) of 227 men with obstructive azoospermia born before 1955, to eight (17 per cent) of 47 men born after 1955.[14] If mercury intoxication is the aetiological factor in Young's syndrome, then it is logical to assume that prevalence of the condition has subsequently declined.

Genetics

Although there has been a reported case of identical twins diagnosed with the condition,[15] no hereditary factors for Young's syndrome have been identified. A positive family history is not indicative of the disease. Genetic studies carried out in Young's syndrome patients found that only a few subjects tested positive for CF transmembrane conductance regulator mutations.[16,17] A link was made in a case report describing Young's syndrome in association with the hereditary disease medullary sponge kidney; the latter disease is characterised by a dilatation of the distal collecting tubules of the kidneys similar to that found in the head of the epididymis in Young's syndrome[18] (due to the accumulation of impacted sperm). This possible genetic link has not been mentioned further in the literature.

Characteristics of Young's syndrome

Young's syndrome affects young males. Sinus symptoms usually disappear after adolescence,[6–8,19,20] whereas pulmonary symptoms may persist. Patients usually seek help for infertility rather than sino-pulmonary problems, and only rarely are patients diagnosed with the condition after initially presenting to an ENT specialist.[7,18,21] Patients frequently give a history of antibiotic treatment for sinusitis, but surgical intervention is not usually required. Young's syndrome is essentially a diagnosis of exclusion in any patient presenting with infertility and sino-pulmonary infections. Handelsman *et al.*[5] identified a cohort of patients with similar characteristics who were considered to have Young's syndrome. All had sino-pulmonary infections, azoospermia with normal spermatogenesis and dilation of the epididymal heads; other conditions such as CF and primary ciliary dyskinesia (then known as immotile cilia syndrome) had been excluded.

In Young's syndrome patients, prolonged nasal mucociliary clearance (tested by placing saccharin on the inferior turbinate) may be the only abnormality identified within the nose, but this finding is not specific for Young's syndrome.[22]

The nasal cilia of Young's syndrome patients have been studied with regard to function and ultrastructure; subtle defects in ciliary structure have been described,[15,23,24] but ciliary beat frequency has appeared normal.[24] Investigators have reported a reduction in the mean frequency of inner dynein arms and an increased incidence of abnormalities of the nine plus two microtubular organisation, when compared with controls. However, the *in vivo* and *in vitro* function of respiratory cilia did not differ from controls.[15] Electron microscopy studies of nasal cilia demonstrated abnormal inner dynein arms when compared with controls.[23] Other studies examining nasal ciliary ultrastructure found normal inner dynein arms but a greater deviation of the ciliary tip, compared with controls.[24] However, it is thought that abnormal mucus accounts for these structural abnormalities rather than a primary ciliary defect.

Diagnostic criteria for sinus disease in Young's syndrome

Over the last decade, attempts have been made to establish ideal diagnostic criteria for both rhinitis and sinusitis. A diagnosis of chronic rhinitis relies on a history of nasal irritation, sneezing, rhinorrhoea and nasal blockage lasting for at least one hour a day on most days. A diagnosis of chronic sinusitis requires two or more of the following symptoms: nasal discharge, nasal blockage or congestion, facial pain or pressure, and reduction or loss of sense of smell. Sinusitis is invariably accompanied by rhinitis; the term 'rhinosinusitis' was therefore recommended by the 1997 Task Force of the Rhinology and Paranasal Sinus Committee.[25] The term 'chronic' implies that symptoms have been present for more than 12 weeks. None of these criteria existed when Young's syndrome was initially described, and the diagnosis of sino-nasal disorders within this cohort of patients has been at best crude.

The most accurate imaging modality for sinusitis is computerised tomography (CT); plain sinus radiographs are unreliable, inaccurate and yield significant numbers of false negative and false positive results.[26,27]

When we considered the accuracy of the diagnosis of sinusitis in patients with Young's syndrome, it became apparent that most authors based their

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diagnosis upon a history of subjective sino-nasal symptoms ($n = 65$ patients).[8,15,17–20,23,28,29] Unfortunately, these publications did not provide precise descriptions of individual symptoms. However, there are reports which describe a history of sinus surgery with positive findings on sinus radiographs, covering a total of 69 patients with Young's syndrome;[5,22,30,31] a further six patients were reported to have undergone sinus surgery without evidence of sinusitis on sinus radiographs.[32,33] Positive findings on sinus radiographs, without any other detail, were described in 19 patients.[2,7,34] Only three patients were reported to have undergone sinus CT scanning.[6] One study conceded that sinus radiographs were abnormal in both patients and controls.[30] Only two reports used a reduction in mucociliary clearance to confirm the diagnosis of Young's syndrome, in 27 patients.[24,35] The most thorough description of sinus disease in patients with Young's syndrome was given by Wang *et al.*,[36] who documented a history of sinusitis, sinus surgery and sinus radiographs, skin prick tests, family history of sinusitis and use of medication that may have affected mucociliary clearance, in four out of 23 patients with obstructive azoospermia.

The respiratory aspects of Young's syndrome have been studied much more extensively. However, we consider that Young's syndrome may have been incorrectly diagnosed in two of the reviewed papers, if it is accepted that sino-nasal disease is a necessary part of the diagnosis: Jequier[37] failed to mention any sino-nasal component in 23 patients, and Khan *et al.*[21] described two patients but reported that nasal mucociliary clearance was normal.

Differential diagnosis

The characteristics of Young's syndrome are similar to those of other syndromes associated with obstructive azoospermia. The differential diagnosis includes CF, congenital bilateral absence of the vas deferens, Kartagener's syndrome and primary ciliary dyskinesia.

Cystic fibrosis

Cystic fibrosis is one of the commonest genetic disorders among Caucasians and affects one in 2500 children.[38] The condition is associated with a defect of the CF transmembrane conductance regulator protein located on the long arm of chromosome seven (ΔF508 mutation is the commonest occurring mutation). Clinically, patients have exocrine pancreatic insufficiency and chronic obstruction and infection of the respiratory tract. These effects are caused by ductal obstruction with thickened, viscous mucus. The obstructive azoospermia is secondary to maldevelopment of the mesonephric ducts, leading to absence or degeneration of the vas deferens, epididymis or seminal vesicles. It is unknown whether this is due to mucus obstruction or secondary to the disease itself.[39] Chronic polypoidal rhinosinusitis is a major component of the syndrome and presents during childhood.[40] Cystic fibrosis has historically been diagnosed using the sweat test, which detects raised concentrations of sodium and chloride in sweat (>40 mm/l in children under 10 years; the test is less conclusive in those over 10 years). More recently, genetic screening has been used to provide more accurate diagnostic information.

Congenital bilateral absence of the vas deferens

Congenital bilateral absence of the vas deferens accounts for up to 2 per cent of male infertility cases,[41] and is considered to be an incomplete form of CF without the pancreatic and respiratory components. This premise is supported by the detection of a similar defect of CF transmembrane conductance regulator protein,[16] but not in all cases; some may have a different, undetected mutation (at present, over 400 different CF transmembrane conductance regulator mutations have been detected). Patients with congenital bilateral absence of the vas deferens may have a positive sweat test, but complete absence of the vas deferens is pathognomonic for the condition. Spermatogenesis is normal among these patients, although the level of sperm antibodies is high.

Primary ciliary dyskinesia

Primary ciliary dyskinesia is an autosomal recessive condition in which abnormal ciliary beating impairs normal mucociliary clearance. Typically, cilia show ultrastructural abnormalities, including inner and outer dynein arm deficiency, microtubular transposition and radial spoke defects.[28] When associated with situs inversus (as occurs sporadically in up to 50 per cent of patients), the condition is known as Kartagener's syndrome. The clinical manifestations of obstructive azoospermia and recurrent pulmonary infections are caused by mucus retention. Nasal nitric oxide production has been shown to be an excellent indicator of primary ciliary dyskinesia; low concentrations are typically observed, compared with controls and patients with other sino-nasal disorders.[28]

TABLE I

KEY DIAGNOSTIC FEATURES OF CONDITIONS CAUSING OBSTRUCTIVE AZOOSPERMIA

Disease	Genetic mutation	Cilia ultrastructure	Saccharin clearance	Nasal NO	Sweat test
Young's	None	Normal	Prolonged	Normal	Normal
PCD/Kartagener's	AR	Abnormal	Prolonged	Low	Normal
CF	AR	Normal	Prolonged	Normal	Abnormal
CBAVD	AR	Normal	Prolonged	Normal	May be abnormal

PCD = primary ciliary dyskinesia; AR = autosomal recessive; CF = cystic fibrosis; CBAVD = congenital bilateral absence of vas deferens

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Patients with obstructive azoospermia of other origin have many clinical features similar to those found in Young's syndrome; however, there is no underlying genetic abnormality associated with the latter condition. The features of Young's syndrome are caused by impairment of ciliary function, rather than a specific anatomical abnormality, and this is probably related to a dysfunction in glycolysis caused by exposure to mercury. Other genetic conditions cause similar abnormalities, but these are due to thickened secretions (e.g. in CF and congenital bilateral absence of the vas deferens) or to abnormal ciliary structure (e.g. in primary ciliary dyskinesia and Kartagener's syndrome) (see Table I).

Summary and conclusions

We can find no convincing evidence that Young's syndrome currently exists. The lack of convincing evidence describing the sinusitic component of Young's syndrome raises doubts over whether the condition remains a true cause of chronic sinusitis.

Although it seems logical to assume that thickened mucus would lead to abnormal ciliary function and thus cause recurrent sinus disease, the actual evidence for this is lacking. It appears more likely that other syndromes associated with obstructive azoospermia are the cause of sinus disease, and these syndromes should be considered instead of Young's syndrome. If the aetiology behind Young's syndrome is mercury intoxication then it would seem likely that the syndrome is in decline, further supporting the view that other syndromes are more common. Further studies are required which are properly designed to accurately diagnose and assess sinus disease in patients with infertility. Such studies should include a thorough sino-nasal history, nasal endoscopy and possibly sinus CT scans. All patients with obstructive azoospermia should be investigated with a combination of NO measurements, sweat testing, ciliary ultrastructure examination and nasal mucociliary clearance time. This would enable an accurate and correct diagnosis in this particular group of patients, and would thus facilitate a deeper understanding of the sino-nasal processes in such infertile patients.

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