Rheum

THE IMPORTANCE OF RARE DISEASES

Day by day those who are obliged to consume their best energies in the frequently so toilsome and exhausting routine of practice find it becoming less and less possible for them, not only to closely examine, but even to understand the more recent medical works.

R.L. Virchow, 1877

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Rare diseases occur frequently! No, not an oxymoron. There are somewhere between 10 and 20 million Americans who are afflicted with a rare disease. In 1985, Congress established the National Commission on Orphan Diseases (NCOD). The NCOD registered approximately 5,000 known rare diseases using a simple definition of a prevalence of less than 1 in 200,000.[1]

Everyone of us in practice has encountered a rare disease. It might be rare by prevalence or incidence (Behcet's disease), rare by geography (malaria at Parkland), rare by association (ankylosing spondylitis with hairy cell leukemia), rare by sex or age (Zollinger Ellison in a 5 year old girl) or rare by specialty (tetralogy of Fallot in rheumatology clinic).

The purpose of this grand rounds presentation is to explore the contribution of rare diseases to the biomedical enterprise through a brief review of four rare diseases. I wish to suggest that lessons learned from the study of rare diseases have contributed more to our understanding of basic processes of disease than might be suggested by their meager prevalence. Further, rare diseases challenge some long held concepts and principles and finally their identification, management and study provide a special opportunity for internists.

RARE DISEASES

1. Usually unknown pathogenesis
2. Too few investigators
3. Under diagnosed or delay in diagnosis
4. Available therapy not generally known
5. Not included in ICD-9 codes

The pathogenesis of rare diseases is usually unknown. The largest group is genetic but even when the gene locus has been identified, the nature of the gene product is unknown and its action at best speculative.

There are too few investigators. Controlled clinical trials cannot be easily accomplished and funding agencies (public and private) are not enamored with tending to the plight of very small populations.

Rare diseases are missed, diagnosed late or misdiagnosed. A third of the patients with rare diseases surveyed indicated that it took from one to five years to obtain a diagnosis and 15% were undiagnosed for six years or more. [2]

Available therapy is generally not known. The Orphan Drug Act has helped here somewhat as have disease registries and vocal lay

groups. Still drug therapies lag behind disease identification and practitioners are far removed from the few skimpy clinical trials being conducted.

These diseases are generally not codable. This is not meant to be a humorous complaint. The reductionist notions of the payor communities and insurance agencies puts patients with rare diseases at double jeopardy. Case reports start with the worst manifestations of the illness. The supposition is then that all individuals with the disease will behave similarly.

I want to review with you the circumstances of four rare diseases. They are Multifocal Fibrosclerosis, Fatal Familial Insomnia, Polymyalgia Rheumatica/Giant Cell Arteritis, and Marfan's syndrome. As an aside, a grand rounds of this nature is fun since there are some in the audience who know more about each of these than I do, no-one knows more about all four (with the possible exceptions of Dr. Foster and Dr. Wilson).

MULTIFOCAL FIBROSCLEROSIS

This is an example of a disease which has slowly come together over many decades. It is a disease affecting several anatomic regions, presenting to a variety of clinical disciplines, unknown in it's etiology or therapy and intriguing in the questions that it raises.

The story begins in 1896 when Bernhard Riedel described a curious form of thyroid disease which he identified in two patients.[3] Both patients had tracheal obstruction caused by densely fibrotic thyroid glands.

Over the decades, additional cases were offered by other clinicians. A consistent clinical and pathologic pattern appeared. Patients are generally female in the fifth decade of life. Most are euthyroid although one third are hypothyroid. The glands when examined are densely fibrotic, infiltrated with a mixed population of B and T cells, and are pathologically distinct from other forms of thyroiditis. Since 1960, thirty four percent of patients with Riedel's thyroiditis have been reported to have one of the other manifestations of multifocal fibrosis.[4,5]

In 1905, Birch-Hirschfeld described pseudo tumor of the orbit. He was an ophthalmologist and his patient presented with unilateral exophthalmos.[6] It is now recognized as the most common cause of unilateral exophthalmos. It resembles an orbital tumor but

pathologically it is a dense fibrotic process with variable inflammatory cells infiltrating the mass. It may result in diplopia, blindness, surgical enucleation or may resolve spontaneously.[7]

The next chapter was written by J.K. Ormond, an urologist who in 1948 described a patient with bilateral ureteral obstruction secondary to dense fibrotic tissue in the retroperitoneum.[8]

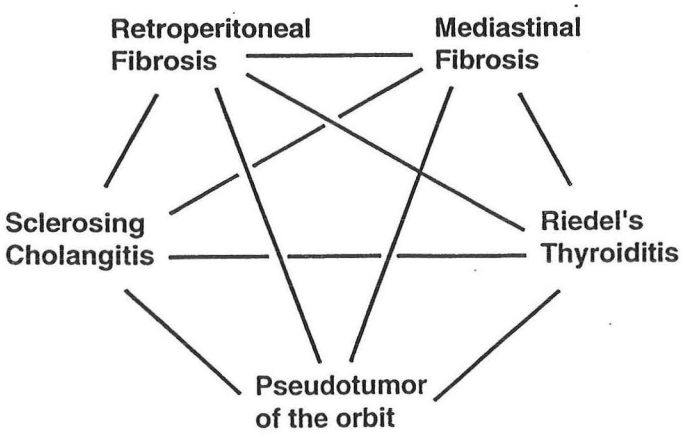
Since then about 500 cases of retroperitoneal fibrosis have been described all showing a dense fibrotic process with a variable component of inflammatory cells and involvement of a variety of retroperitoneal structures. Obstructive uropathy is the most consistent clinical presentation.[9]

A striking number of patients had exposure to methysergide, a congener of LSD which blocks receptors for 5 HT and was used as a therapy for migraine headaches.[10] There was sufficient data of an association that the drug was withdrawn by the FDA.

Similar pathologic processes have been described in the mediastinum, meninges and the liver as sclerosing cholangitis (without inflammatory bowel disease, Dr. Magee).[11,12]

The etiology of these conditions is unknown. There is no single diagnostic test and the pathology while somewhat distinctive is rather bland. How then are they grouped to represent a common entity? It is a case of guilt by association.

Each of these conditions, rare in their own right, has been described in association with each of the others with the exception of the pachymeningitis which occurred in an individual with orbital pseudo tumor and sclerosing cholangitis. The term multifocal fibrosclerosis probably belongs to David Comings. [13]



(?) Cranial pachymeningitis

This is an example of the piqued curiosity when two or more rare diseases occur together. What can we learn and what questions can we ask?

MULTIFOCAL FIBROSCLEROSIS

1. What is the pathogenesis?
2. What is the relationship to serotonin?
3. Why midline structures?
4. Is fibrosis the disease or result?
5. What can we learn about scars, adhesions, keloids, burns, and P.S.S.?

What is the pathogenesis? Suggested mechanisms include vasculitis, genetics (reported in two brothers of a consanguineous marriage), and immunologic.

No typical picture of vasculitis has been reported, no antigen, immune complex or cell mediated mechanism has been elucidated and no genetic studies have been done.

The reports of an association with methysergide are curious in light of other associations of fibrosis with disordered serotonin metabolism. Methysergide is an antagonist at receptors for 5 Hydroxy-tryptophane. When the drug was discontinued the retroperitoneal fibrosis reversed in many cases. We are reminded of the fibrosis which occurs in carcinoid syndrome with its attendant mesenteric, pleuropulmonary and endocardial fibrosis. Is there a link here? Would you be bold enough to try octreotide for therapy?

Why should these particular anatomic sites be preferred? Why are the heart, lung, kidneys, synovium or other organs not involved? In carcinoid, the left heart is thought to be protected because of some degradation of the offending hormone through the lungs and the full syndrome does not occur unless tumor is present in the liver bypassing that organ's detoxification engines.

Is the fibrosis the disease or only the remnant? We understand from wound healing how scarring is the last component of the process. Was there an antecedent in the asymptomatic period that went undetected?

Scarring and fibrosis is an ubiquitous process. If we understood the mechanisms of this rare disease, would it help us understand keloids, adhesions, Peyronie's, burns and progressive systemic sclerosis?

FATAL FAMILIAL INSOMNIA

Isn't that an awful sounding disease? Can you imagine not sleeping to death? The first report of this rare disease appeared in an abstract by Italian physicians.[14] They recognized they had uncovered a new disease but were perplexed about its etiology suggesting that it might be viral. Later they noted some similarities to the spongiform encephalopathies and several years later concluded that it represented a new variety of prion disease. [15,16]

The original family suffered from extreme sleep disturbance including progressive reduction of nocturnal sleep with dysnomia, confusion and oneirism.

These were followed by thermoregulatory disturbances, altered respiratory patterns, miosis, sphincter dysfunctions, tremor, ataxia, dysarthria and myoclonus with eventual coma and death. Five families have now been described with this disease. The mean age at onset is 51 with a mean duration of symptoms of 14 months. Of interest, global intelligence is preserved. The prion genetics of this disease have now been established.[17]

The history of the prion diseases makes for fascinating reading. Creutzfeldt first described a spongiform encephalopathy in 1920 and was soon echoed by Jakob in 1921.[18,19] Creutzfeldt's case was a 22 year old woman with a progressive dementing illness. Jakob described four older patients with progressive dementing illness.

As more cases were described, a consistent clinical pattern emerged of aggressive dementia at a relatively young age, many with cerebellar dysfunction and nearly all with myoclonus.

Next came Gerstmann-Staussler-Scheinker syndrome in 1928. A disease characterized by slowly progressive ataxia with various degrees of mental decline usually lasting 2-10 years.[20]

Gajdusek stirred the pot with his description of kuru, a rapidly fatal disease with severe cerebellar ataxia epidemiologically linked to the practice of cannibalism. [21]

In 1959, Hadlow described the pathologic similarities between kuru and scrapie, a known infectious disease of sheep and goats, and he suggested that kuru might be transmissible to laboratory animals. During the next few years kuru, GSS and CJD were transmitted to apes and monkeys. [22]

To this day confusion exists. With the evidence of transmissibility to primates of course an infectious etiology was the likely cause. This was further supported by the kuru story and the transmission of CJD by corneal transplantation and the use of neurosurgical instruments.

Confounding the infectious disease camp were the strong family pedigrees of CJD, GSS and FFI. Further confounding them was the peculiar nature of the infectious agent. Curiously, it was protease resistant, UV resistant and devoid of any nucleic acid. What could be going on here?

Pruisiner challenged traditional wisdom by suggesting the term prion for protein-infectious agent. Vitriol followed in the literature but vindication followed. [23]

What we now know prompts as many questions as are answered. Prion is a naturally occurring brain protein coating neurons. Its genetic instructions are on the short arm of the 20th chromosome. All forms of the spongiform encephalopathies result from abnormalities of this protein. With single amino acid substitutions, the protein folds abnormally - sort of a sickle cell of the brain.

Introduced or "infective" prions behave like seed crystals causing a cascade of folding errors in adjacent, otherwise normal, prion proteins. Either the function of the normal prion is disturbed or the abnormal configuration leads to cell damage.

HUMAN PRION DISEASES

Disease	Etiology
Kuru	Infection
Creutzfeldt-Jakob disease	
Iatrogenic	Infection
Sporadic	Unknown
Familial	PrP mutation
Gerstmann-Sträussler-Scheinker disease	PrP mutation
Fatal familial insomnia	PrP mutation

Now the really intriguing feature. It turns out that both FFI and CJD have the same point mutation at codon 178. The only difference is that patients who develop FFI have methionine coded at 129 while those with CJD code for valine at 129! [24]

PRION DISEASES

1. What do we mean by "infectious disease"?
2. What other illnesses are caused by protein folding abnormalities?
3. How do you treat a folding error or prevent "seed crystals"?
4. Why should a single A.A. substitution cause havoc in variable regions of the brain?
5. Are there clues to other dementias?
6. What is the function of normal prion protein?
7. How does infectious protein get into the brain?
8. What does the thalamus have to do with autonomic function?
9. Is there a lesson for other dementias?

What exactly do we mean by infectious disease? Can a seed crystal be called an infectious agent? Transmissible prion spongiform encephalopathies fulfill Koch's postulates yet it stretches our traditional thinking about infectious agents.

What other diseases are caused by protein folding abnormalities? The rules of protein folding are the cause of great investigative interest currently. Perhaps when we know how the sequence determines folding we shall understand many other genetic processes both normal and abnormal and the potential for pharmaceuticals could be extraordinary.

Are there any treatment protocols for folding errors or protections from damaging crystals? Is the folding or slinky effect determined by the chemical soup in which it occurs?

Why should a single amino acid substitution coupled with a single polymorphism present with such strikingly different clinical manifestations? Other than being brain diseases of a spongiform nature, the picture of FFI could not be confused CJD. If the prion protein is ubiquitous in the brain, why should perturbations be selective in the areas of the brain affected?

What does FFI tell us about thalamic function? The thalamus

does not stand tall in the investigations of autonomic function or sleep. Is the thalamus a transit point or a center of function?

What, if anything, is the relationship of the spongiform encephalopathies with dementia to Alzheimer's dementia? Some, but not all cases of the spongiform encephalopathies, demonstrate amyloid plaques. Both occur sporadically and in families. In both, an abnormal form of a neuronal protein appears to play a key role. Alzheimer's has not been transmitted to primates. [25]

The backdoor may yet be open, however. The Apolipoprotein allele thought to be a risk factor for Alzheimer's disease has been shown to also be a risk factor for the development of CJD and in determining its severity. [26]

MARFAN'S SYNDROME

This is the least rare of the diseases I want to discuss. Most everyone in this audience has seen at least one case of Marfan's and most would be able to diagnose it after a single office visit. Notice, however, that it is still an eponymic entity and it still has the appellation of syndrome rather than disease.

As with many rare diseases, we describe them by the original author. Also, the introduction of a new disease is frequently descriptive and lacking in a single diagnostic test. Until our corporate wisdom allows us to feel certain that we have a distinct entity we take comfort in the term syndrome rather than disease.

Certainly, Marfan's should now be called disease; and it might even be called fibrillin disease.

> I present to the Society a little girl five and one-half years old, suffering from a congenital deformation of the four limbs, for which I have not found a precedent from the authors whom it was possible for me to consult.
>
> A-B. Marfan, 1896 [27]

Marfan, a Parisian Professor of Pediatrics, presented his case at a local medical society meeting. He was curious about the etiology and is quoted to have said "...I beg my colleagues to tell me if they have seen analogous cases." This is the plea of all case reports.

Importantly, Marfan continued to care for and observe his patient. When his little patient was 11, he reported radiographs

showing kyphoscoliosis and the first signs of tuberculosis which was to eventually kill her.

Marfan preferred the term dolichostenomelia and by 1938 he reported that more than 150 cases had been described and that the process involved several organ systems. He also recognized the dominant Mendelian characteristics of the disorder. [28]

MARFAN'S SYNDROME

1. Skeletal
2. Ocular
3. Cardiovascular
4. Pulmonary
5. Skin and integument
6. Central nervous system

The syndrome became widely described and characterized and therapeutic measures for the most dramatic consequences of cardiovascular involvement appeared but the etiology defied discovery.[29]

Marfan himself mused over the possibility of a mesodermal disorder but noted that the ocular lens was of ectodermal origin. Likewise he considered but discarded an abnormality of pituitary function which had been suggested because of the physical likeness to prepubertal eunuchs.

Connective tissue diseases received great attention over the last three decades. Investigators began to delight in understanding the nature of our scaffolding and in particular collagen. A family of more than 15 different types of collagen have now been described in association with several structural diseases including osteogenesis imperfecta, Ehlers-Danlos syndrome and the several chondrodysplasia. The genetic mutations have been characterized, and similar to the folding problem described for the prion diseases, we now know that the disorders of collagen are marked by changes in repetitive sequences that lead to triple helix structures characteristic of collagen. [30]

Other support elements came under scrutiny. Proteoglycans and glycosaminoglycans, the ground substance was suspect because of the pathology in the aorta.[31] Similar pathology was detected in lathyrism, however, which disrupts cross linking of elastin. [32]

Roark finally suggested that the basic defect was in elastic fibers. The two major components of elastic fibers are an amorphous core of elastin and a matrix of structured microfibrils.[33]

The hunt was on. Nay-sayers were convinced that the disorder was not a single gene defect. Laboratories working in concert had, by the mid 1990's, excluded 94% of the human genome - an approach that would have continued to fail if, indeed, the defect was heterogenous. The authors deserve credit for negative results - painful![34]

Finally, in 1991, the culprit was identified. Marfan's syndrome was mapped to the short arm of the 15th chromosome. The lod score is now over 40 and the gene has been mapped in situ - a point mutation in the coding sequence for fibrillin.[35]

Fibrillin function is being teased out, much of it suggested by the phenotypic expressions of Marfans. Microfibrils serve as scaffolding for the deposit of elastin as well as to linking elastic fibers to each other and other components of the extracellular matrix. Second, microfibrils can support the attachment of vascular smooth muscle cells, and finally they have the ability to alter cellular activity. [36]

MARFAN'S SYNDROME

1. What is common to homocysteinuria?
2. Why are the manifestations variable?
3. What does this tell us about aneurysms?
4. What is the role of fibrillin in aging?
5. Are dominant structural diseases amenable to cure?

The manifestations of homocysteinuria are sometimes confused with Marfan's syndrome although the thrombotic and mental retardation tendencies are clearly distinct. The microfibrillar structures are shattered, presumably due to disruption of the disulfide bridges. The category of Vitamin B6 responsive patients with homocysteinuria is particularly curious and might suggest new modalities for Marfan's patients.

Why are the manifestations variable? The nature of the point mutation is variable and once again it is curious that a single variable amino acid should cause such a variability in clinical expression. What other factors are at play?

Are there lessons here for other aneurysms - aortic, cerebral, aneurysms of pregnancy and aneurysms of injury? Similarly, we might profitably explore the role of fibrillin in other common connective tissue disorders such as osteoporosis, osteoarthritis, and aging - the most common connective tissue disease.

Are any of the dominant structural diseases amenable to cure? How do you replace the girders in a falling skyscraper?

POLYMYALGIA RHEUMATICA/GIANT CELL ARTERITIS

> The red cell sedimentation "...reaction can be regarded as reflecting the intensity of exudative inflammation (or of destructive processes). A pathologic sedimentation reaction value, however, may occur in nearly all sorts of diseases, the test being in this respect rather like fever and leukocytosis; for instance, the highest figures (above 100 mm) are found in such conditions as lobar pneumonia, rheumatic polyarthritis, certain forms of nephritis, etc.... A normal reaction is, of course, met with in all sorts of functional disease, but a normal sedimentation reaction does not at all exclude an organic disease..."
>
> Alf Westergren, 1926

This entity is the fourth of my selection. It is not extremely rare but sufficiently uncommon and singular in its lessons that it is worth a few minutes discussion.

A personal experience includes a 78 year old retired tailor who came to the office because of palpitations, breathlessness and fatigue. He was in atrial fibrillation and congestive heart failure. He was admitted for therapy of the failure and rate control. He also complained of headache, loss of appetite, and occasional feverish feeling. Routine laboratory evaluation disclosed a mild normochromic normocytic anemia and slightly elevated alkaline phosphatase and was otherwise normal although a sed rate was not performed - (why should it be, this was a cardiac problem!)

On the second hospital day, he suffered severe chest pain, showed an acute myocardial infarction on the electrocardiogram, had electro-mechanical dissociation and died. An autopsy disclosed giant cell arteritis of the coronary arteries in two locations as

well as involvement of the aortic arch. The temporal arteries were not examined.

EPIDEMIOLOGY OF GIANT CELL ARTERITIS

Peak incidence at ages 60-75
Sex distribution of 3 women to 1 man
Annual incidence 18/100,000 people aged over 50
Prevalence 223/100,000 people aged over 50*
Most reports from northern Europe and northern United States; mainly affects white people, but can occur worldwide
Familial aggregation has been reported, suggesting genetic association

*Diagnosis confirmed by biopsy

INITIAL SYMPTOMS (n = 49)

	n
Headache	29
temporal	13
parieto-occipital	5
retro orbital	5
diffuse	6
Jaw claudication	7
Other neurologic symptoms	
Diplopia	4
Amaurosis fugax	4
Persisting amaurosis	1
Deterioration of vision	5
Postural vertigo	6
Polymyalgic and diffuse symptoms	
Symmetric myalgias shoulders	34
Symmetric myalgias thighs	34
Morning stiffness of the joints	35
Distal myalgias	13
Lack of appetite/loss of weight	28
Subfebrile temperatures	13
Depressive syndrome	9
Diarrhea, vomiting	2
Syncope	1
Occlusive arterial disease of the legs	1
Sjögren's syndrome	2

INITIAL LABORATORY FINDINGS

	Total Collective (n = 49)	PMR (n = 30)	AT (n = 10)	PMR/AT (n = 9)
ESR (mm/h)	86	81	96	93
CRP (ng/dl)	5.4	6.0	3.1	4.4
Anemia (Hb < 12 g/dl; RBC < 4 million/mm3	35%	30%	40%	44%
Cholestatic hepatopathy	28%	13%	22%	71%
Autoantibodies (ANA, granuloplasma antibodies)	8	7	1	---
Rheumatoid factor (Waaler-Rose)	3	3	---	---

The disease is of the elderly and has a predilection for women. It is rare in African Americans.

Most complain of temporal headache, occasional with scalp tenderness but other unusual symptoms include jaw claudication, amaurosis fugax, and constitutional symptoms.

The pathology is fairly characteristic. An inflammatory infiltrate involves the internal elastic lamina with disruption and lumen narrowing. Giant cells are prominent in the infiltrate and in this regard the disease somewhat resembles Takayasu's disease - this entity occurs in younger patients usually women and has a different clinical spectrum. Giant cell arteritis prefers vessels with an elastic lamina and rarely involves intracranial vessels or others scarce in this substance. The pathology is the gold standard of diagnosis. [37]

The curious stablemate of this disorder is polymyalgia rheumatica (PMR). The two often occur together in the same patient either at the same time or at disparate intervals. PMR is a very curious syndrome. The usual patient is once again an elderly woman. The complaints are frustrating, mundane and common - lassitude, pelvic and pectoral girdle myalgias, occasional low grade fever, and perhaps a mild weight loss. When mild, it suggests the "fatigue of age" and when severe it suggests an occult malignancy.

The diagnosis is once again a syndrome with the keystone being a markedly elevated sedimentation rate, frequently above 80 mm/hr. Often there will be a mild normochromic normocytic anemia and mild elevations of the alkaline phosphatase. The best diagnostic test

is the response to corticosteroids which generally affords dramatic relief within days. Unlike giant cell arteritis, there is no diagnostic pathology. Muscle enzymes, biopsies, electromyography and imaging have not shown any specific pathology.[38]

The association of the two diseases in some patients and not in all, cannot be explained.

DEMOGRAPHIC DATA OF FOLLOW-UP GROUP
(49 PATIENTS WITH GIANT CELL ARTERITIS)

20 men, average age 67.9 years at onset of disease
29 women, average age 70.8 years at onset of disease
PMR n = 30 (13 men, 17 women, average age 70 years)
AT n = 10 (4 men, 6 women, average age 67.7 years)
PMR/AT n = 9 (3 men, 6 women, average age 70.6 years)
Temporal artery biopsy n = 17, positive n = 14
Time between first symptoms and diagnosis 3.7 months
(range 1-22 months)
PMR mean 4.4 months
AT mean 3.1 months

Other than a very high sedimentation rate and a dramatic response to steroids, they share few features in common.

Is there a common circumstance, genetic or antigenic, which predisposes to both illnesses? Does having one present a risk factor in itself to the development of the other?

PMR/GCA

1. Why do they co-exist?
2. Why do they not co-exist?
3. Why are specific vessels involved?
4. Why is this a disease of the elderly?
5. Why is the ESR so sensitive?
6. What is the pathogenesis?

Do these diseases have a unifying cause? Is there some phenomenon which leads to both? The sedimentation rate (and convincing evidence that the C reactive Protein level) is curiously

sensitive to these disorders. This long maligned test of high sensitivity and very low specificity in these disorders, at least, is the major ally of therapy. It causes us to revisit the nature of the "acute phase reactants" that we poorly understand and have worried about since Westergren devised his test early in this century. [39] Is the cause somewhere in this soup?

What is the etiology? It was briefly suggested that GCA was an actinic disease, affecting the temporal arteries because of sun exposure. Quickly dispelled, other theories have been suggested. Many patients have antibodies to Borrelia and a few give histories of tick bites. One case report alleged to have found Borrelia antigen in a biopsy specimen. Immune mediated damage is attractive. Complement and antibody complexes have been demonstrated in a few lesions but not all. No antibodies to components of elastin have been found.

ETIOLOGY OF POLYMYALGIA RHEUMATICA
AND GIANT CELL ARTERITIS

There is often a distinct prodromal event
resembling influenza, but results of viral
studies are negative
Lymphocytes in arteritic lesions express the T cell phenotype,
and the CD4 subset predominates
Frequency of HLA-DR4 is increased

EVIDENCE FOR GENETIC COMPONENTS IN GCA/PMR

Familial aggregation
Non-random geographic distribution with highest incidence in
Northern whites
Female preponderance
HLA-DR association

More commonly detected in the lesions are CD4 cells. The majority of patients express the B1*0401 or B1*0404/8 variant of the HLA-DR4 haplotype. The response to steroids suggest and immune mediated action.[40] Still there are those nasty giant cells as in sarcoid and tuberculosis.

Whatever the hypothesis, it will have to account for the co-existence of these two disorders, the female predominance, the age discrimination, the vessel specificity, the dramatic response to steroids and the identification of the unknown reactive protein.

LESSONS

Each of these examples was selected not just for curiosity sake but because each provides a lesson in medical science.

Multifocal fibrosclerosis reminds us of the problems of specialization. This disease with its habit of disturbing different organ systems is likely to show up in a variety of specialists' offices. It is likely that there are other diseases of this variety out there which because of our inability to look over the fence of our colleagues we have not recognized as being in a family or of similar pathogenesis. Once in a while, it would be good to nourish story swapping - attending a grand rounds in another specialty or picking up an unfamiliar journal in the library or having lunch with clinicians of other stripes.

Marfan's disease was selected as an example of careful investigation of a single case with follow up. Importantly, this disorder described clinically, provided the raw material for the basic scientists to study and comprehend some very basic important processes and substances. The case report and the rare disease replenish the aquifer of basic science often with no prediction of where the springs will come forth. This is a critical part of the fertile feedback loop between clinicians and basic scientists.

Fatal Familial Insomnia shows how an exceedingly rare disease can influence some of our most basic notions of health and disease. We thought we understood infectious diseases - we don't. We are challenged to think more clearly about structural protein pathogenesis and are reminded of how little we really know about brain function.

PMR/GCA reminds us of the unusual disease hiding in common clothes. Who here would have predicted that this malady was hiding in the myriad of old folks with diffuse aches and pains, that it could take a headache and explode it to blindness or myocardial infarction, and who lives comfortably with the notion that we have seen this and not recognized it in some patients?

SPECIAL LESSONS FOR THE INTERNIST

Patients with rare diseases come to your office. How do you know you have one?

RECOGNIZING A RARE DISEASE

1. When you consider two diseases
2. Wrong age or sex
3. Curious family history
4. Strange lab result
5. Lack of expected therapeutic response
6. When you want two or more consultants (or you don't know who to ask)
7. It doesn't feel right

Lots of our patients have more than one disease but when you consider two disparate entities in the same patient it might be a clue that you have a single unusual disease.

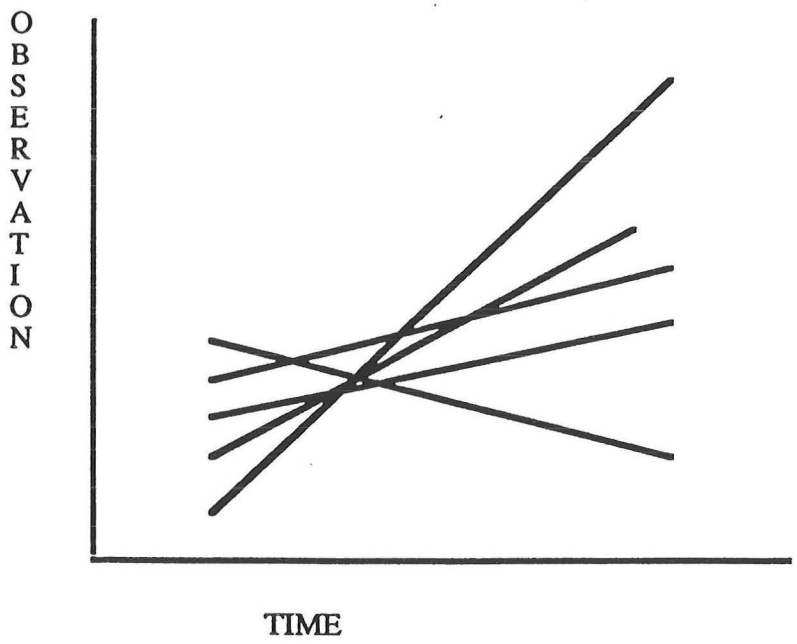
If you find yourself making a diagnosis that is not comfortable with the age of the patient or the gender it may be a clue that you have a different disorder.

Don't discount the bizarre family history that some patients will tell you. We sometimes believe that the history of family illness, especially when it was many, many years ago was the product of story telling or the ignorance of physicians of that era. It just might not be.

What do you do with the lab result which is a surprise and one you really didn't ask for but it came in the panel. Is it a lab error or do you discount it because it is solitary - it may be worth thinking about or consulting the library. Likewise if your therapeutic program doesn't work or it backfires it may be that the patient doesn't have the illness you thought. If you are inclined to ask the advice of two or more consultants or just don't know which consultant to ask, you may have a rare disease. Finally, the age old admonition of paying attention to your gut instinct if it "just doesn't feel right".

I may not know how to always spot the rare disease, but there are a few circumstances which will guarantee that they are missed. Beware the creeping sensation that "all my patients are alike" or the cavalier, "just another day of weak, tired and dizzy patients".

This is fostered by inadequate time with the patient and the reductionistic environment of disease that we find ourselves in. I am not suggesting that every patient should be "trolled through the lab to see who bites" or that the mega workup is the road to assurance. Rather, a modicum of attention and skepticism can provide great pleasure in the diagnostic hunt.



This is the type of chart that appeals to the clinical research team. An intervention is done, the results plotted and the probability that they are associated is calculated. My interest is in the one contrary patient. Why did he/she behave differently? This patient deserves special attention. This is the genesis of the case report and I hope to have convinced you of the utility of investigating the rare disease.

REFERENCES

1. The Orphan Drug Amendments of 1985. Public Law 99-91. Washington, D.C. August 15, 1985.
2. Report of the National Commission on Orphan Disease. Publication No. HRP-0907248. Springfield, Virginia. National Technical Information Services. April, 1989.
3. Riedel BMCL. Die chronishe, zur Bildung eisenharter Tumoren fuhrende Entzundung der Schilddruse. Verh Dtsch Ges Chir 25:101-105, 1896.
4. Schwaegerle SM, Bauer TW, Esselstyn CB. Riedel's Thyroiditis. AJCP 90:715-722, 1988.
5. Bartholomew LG, Cain JC, Woolner LB et al. Sclerosing Cholangitis; Its possible association with Riedel's struma and fibrous retroperitonitis. Report of two Cases. NEJM 269:8-13, 1963.
6. Birsch-Hirschfeld A. Zur Diagnostik und Pathologie der Orbitaltumoren. Ber Deutsch Ophth Ges Heidelberg. 127, 1905.
7. Miller E, Weissler MD, Fortune MA. Sclerosing Orbital Pseudo tumor: A unique clinical entity. Ann Otol Rhinol Laryngol 98:496-501, 1989.
8. Ormond JK. Bilateral Ureteral Obstruction due to envelopment and compression by an inflammatory retroperitoneal process. J Urol 59:1072, 1948.
9. Jones JH, Ross EJ, Matz LR, Edwards D, Davies DR. Retroperitoneal fibrosis. Am J Med 48:203, 1970.
10. Koep L, Zuidema GD. The clinical significance of retroperitoneal fibrosis. Surgery 81:250, 1977.
11. Barret NR. Idiopathic mediastinal fibrosis. Brit J Surg 46:207, 1958.
12. Berger JR, Snodgras MD, Glaser J, et al. Multifocal fibrosclerosis with hypertrophic intracranial pachymeningitis. Neurology 39:1345-1349, 1989.
13. Comings DE, Skubi KB, Van Eyes J, Motulsky AG. Familial Multifocal Fibrosclerosis. Ann Intern Med 66:884-892, 1967.
14. Medori R Gambetti P, Cleveland OH, et al. Familial Progressive Insomnia. Impairment of the Autonomic Functions, Degeneration of Thalamic Nuclei: A New Disease? Neurology 35(suppl):145, 1985.

15. Lugaresi E, Medori R, Montagna P, et al. Fatal Familial Insomnia and Dysautonomia with Selective Degeneration of Thalamic Nuclei. NEJM 315:997-1003, 1986.
16. Gambetti P, Petersen R, Monari L, et al. Fatal Familial insomnia and the widening spectrum of prion diseases. Brit Med Bull 49:980-994, 1993.
17. Bellows JG. Conspectus, One genetic Mutation, Two Diseases. Comprehensive Therapy 19:3, 1993.
18. Creutzfeldt HG. Uber eine eigenartige headformige erkrankung des zentral nerven systems. A Gestamte Neukrol Psychiatrie 57:1-18, 1920.
19. Jakob A. Uber eigenartige erkrankungen des Zentral nerven systems mit bemerkenswertem anatomischen befunde. A Gesamte Neurol Psychiatrie 64:147-228, 1921.
20. Farlow MR, Tagliavini F, Bugiani O, Ghetti B. Gerstmann-Straussler-Scheinker disease. In: Handbook of Clinical Neurology. Amsterdam: Elsevier pp:619-633, 1991.
21. Klatzo I, Gajdusek DC, Zigas V. Pathology of kuru. Lab Invest. 8:799-847, 1959.
22. Gibbs CJJ, Gajdusek DC, Asher DM. Creutzfeld-Jakob Disease: Transmission to the chimpanzee. Science 161:388-89, 1968.
23. Prusiner SB. Biology and Genetics of Prion Disease. Ann Rev Microbiol 48:655-686, 1994.
24. Bellows JG. One genetic mutation, Two Diseases: Fatal Familial Insomnia and Creutzfeldt-Jakob Disease. Compr Therapy 19:3, 1993.
25. Brown P, Kaur P, Sulima MP, et al. Real and imagined clinicopathogical limits of "prion dementia". Lancet 341:127-130, 1993.
26. Amouyel P, Vidal O, Launay JM, et al. The apolipoprotein E alleles as major susceptibility factors for Creutzfeldt-Jakob disease. Lancet 344:1315-1318, 1994.
27. Marfan A-B. Un cas de deformation congenitale des quatre membres plus prononcee aux extremites caracterisee par l'allongement des os avec un certain degre d'amincissement. Bull Mem Soc Med Hop Paris 13:220-226, 1896.
28. Marfan A-B, La dolichostenomelie. Ann Med 44:5-29, 1938.

29. Pyeritz RE. The Marfan Syndrome. Connective Tissue and Its Hereditable Disorders. pp. 437-468, 1993 Wiley-Liss, Inc.
30. Prockop DJ. Mutations in Collagen Genes as a Cause of Connective Tissue Diseases. NEJM 326:540-546, 1992.
31. Hurley JV. Marfan's Syndrome: The Nature of the aortic defect. Aust Ann Med 8:45-540, 1959.
32. Fornieri C, Baccarani-Contri M, Quaglino D, et al. Lysyl Oxidase activity and elastin/glycosaminoglycan interactions in growing chick and rat aortas. J Cell Biol 105:1463-1469, 1987.
33. Roark JW. The Marfan Syndrome: Report of one case with autopsy, special histological study and review of the literature. Arch Intern Med. 103:123-132, 1959.
34. Blanton SH, Sarfaarazi M, Eiberg H, et al. An exclusion map of Marfan syndrome. J Med Genet 27:73-77, 1990.
35. Dietz HC, Pyeritz RE, Hall BD, et al. The Marfan syndrome locus. Genomics 9:355-361, 1991.
36. Kielty CM, Shuttleworth CA. Fibrillin-containing Microfibrils: Structure and Function in Health and Disease. Int J Biochem Cell Biol 27:747-760, 1995.
37. Huston KA, Humnder GG, Lie JTT, et al. Temporal arteritis; a 25 year epidemiologic, clinical and pathologic study. Ann Intern Med 88:162-167, 1978.
38. Chuang T-Y, Hunder GG, Ilstrup DM, et al. Polymyalgia rheumatica: A 10 year epidemiologic and clinical study. Ann Int Med 97;672-680, 1982.
39. Zlonis M. The mystique of the erythrocyte sedimentation rate. Clinics in Lab Med 4:787-801, 1993.
40. Hunder GG, Lie JT, Goronzy JJ, Weyand CM. Pathogenesis of Giant Cell Arteritis. Arth Rheum. 36:757-761, 1993.