Housecalls

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INSIDE THIS ISSUE

ON THE RISE

Autoimmune Diseases

In this issue of *Housecalls* Dr. Regina Rosace presents a case of Attention Deficit Hyperactivity Disorder (ADHD) while I discuss a case of Granulomatosis with Polyangiitis (GPA). GPA is a rare autoimmune disease that can damage several major organ systems.

Unfortunately, autoimmune diseases are on the increase in many parts of the world. Autoimmune diseases result from a pathologic attack by the body's immune system against an antigen present as part of the molecular structure of the host. Autoantibodies are not uncommon in immunologically intact people, and even with autoimmune diseases, they can exist for many years prior to the onset of disease.

Studies in identical twins indicate that underlying genetically heritable traits account for less than half of the susceptibility to autoimmune diseases. Epigenetic influences on gene expression, infections, environmental factors and even the personal microbiota have all been shown to influence the development of various autoimmune diseases. Examples of diseases with actual or presumed autoimmune basis are Type 1 diabetes, systemic lupus erythematosus, myasthenia gravis, autoimmune thyroiditis, autoimmune hepatitis, bullous pemphigoid, celiac disease, GPA, etc.

A recent review of 30 articles revealed an estimated annual percent increase in rheumatic, endocrine, gastrointestinal and neurological autoimmune disease of 7.1, 6.3, 6.2 and 3.7%, respectively. If there is any bright spot in this trend of increasing autoimmune diseases it is the development of better immunosuppressive and immune modulating drugs. Newer biologic agents are targeting specific inflammatory and immune reactions, thereby lessening the potential damage to healthy tissue. Meanwhile the genetics, precursors, causes and triggers of autoimmune disease is an active area of medical research.

REFERENCES

Bach J, "The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases," N Engl J Med 2002; 347:911-920.

Lerner A, et al, "The World Incidence and Prevalence of Autoimmune Diseases is Increasing" Int J of Celiac Dis 2015;3(4):151-155

SCOR
The Art & Science of Risk

CASE #1

Granulomatosis with Polyangiitis

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A 23-year-old male applied for life insurance. He reported being diagnosed with Wegener's Granulomatosis about nine months prior to the application. He presented with swelling of his ankles and knees and was admitted to the hospital where he was treated with Intravenous fluids, then discharged and placed on oral meds for eight months with resolution of symptoms. He reported that he is now off all medications and asymptomatic. No APS was obtained.

What is Wegener's Granulomatosis, and what are the mortality implications?

The disorder called Wegener's Granulomatosis was renamed in 2011 by the American College of Rheumatology and the European League against Rheumatism. They suggest the new name of granulomatosis with polyangiitis (GPA). GPA is a rare disease with an estimated prevalence in the United States of 3 per 100,000 people. The prevalence in the U.K. is estimated at 25 per 100,000. Ninety percent of cases occur in persons of northern European descent. There is a male to female ratio of approximately 1.5 to 1. Patients with GPA typically present between the ages of 35-55 years; however, it can occur at any age, even in children.

GPA is considered to be one of a family of small vessel vasculitides that are associated with anti-neutrophil cytoplasmic autoantibodies (ANCA). Other disorders in this group include microscopic polyangiitis (MPA) (including renal-limited vasculitis (RLV)) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss). In addition to the ANCA association, these disorders share a similar renal histology characterized by a focal, crescentic glomerulonephritis.

The pathology of the vasculitis associated with MPA, GPA and EGPA is indistinguishable. EGPA may be associated with asthma and eosinophilia, is the least common of the ANCA-associated vasculitides and has a different prognosis. It is beyond the scope of this discussion.

People with GPA or MPA often present with fatigue, fever, weight loss and anorexia. Prior to the development of ANCA testing the diagnosis of Wegener's was based on clinical criteria such as oral or nasal inflammation characterized by ulcers or bloody nasal discharge; abnormal chest x-ray showing granulomas (nodules) or cavitations; microscopic hematuria and proteinuria; and biopsy evidence of granulomatous inflammation of a small artery.

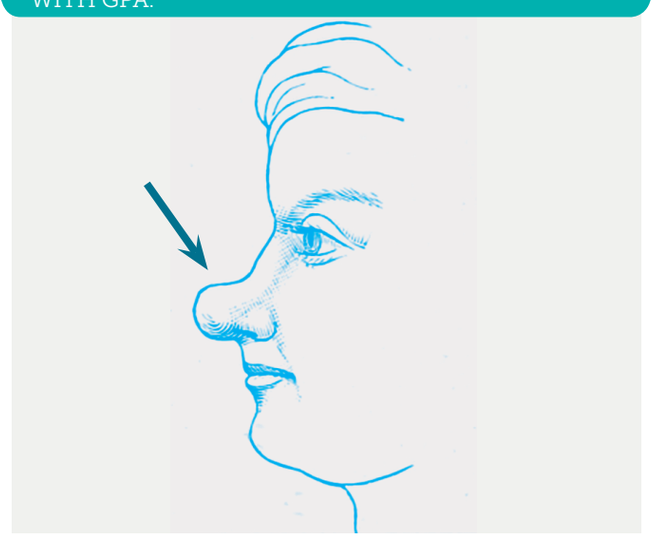
The inflammation in the nose can destroy underlying supporting structures and result in a characteristic saddle deformity **(Figure 1).** In theory MPA is differentiated from GPA by the lack of granulomatosis; however, biopsies can miss areas of involvement. There is often overlap in clinical findings, and even progression from MPA to GPA has been noted.

About 90% of people with GPA will have detectable ANCA; for patients with MPA the number is closer to 70%.

About 90% of people with GPA will have detectable ANCA; for patients with MPA the number is closer to 70%. The subtype of ANCA can also be used to differentiate MPA from GPA. There are two primary neutrophil autoantigens; Myeloperoxidase (MPO) found in approximately 10% of ANCA positive patients and Proteinase 3 (PR3) found in 80-90% of ANCA positive patients. With cellular staining, the MPO antigens are found in a perinuclear pattern (P-ANCA), while PR3 antigens are in the cytosol (C-ANCA). PR3-ANCA is primarily associated with GPA, while MPO-ANCA is associated with MPA.

There is some evidence that the type of ANCA may be more predictive of outcome than the diagnosis of GPA or MPA. There are various guidelines of diagnostic criteria and algorithms to establish the diagnosis of GPA, and there is currently a large multi-national study to better define all of the vasculitides. But, elevated titres of PR3-ANCA and biopsy or typical imaging evidence of granulomatous inflammation on medium to small arteries are generally accepted as diagnostic of GPA.

FIGURE 1 – A CHARACTERISTIC SADDLE DEFORMITY OF THE NOSE CAN OCCUR IN UP TO 28% OF PEOPLE WITH GPA.



Treatment & Prognosis

Early treatment is important for preventing organ damage and may be life-saving, but skin, lung or kidney biopsy confirmation remains the most definitive method to establish the diagnosis.

The natural history of GPA was grim prior to the advent of effective therapy. The mean survival was approximately five months. Eighty-two percent died within the first year and a cumulative 90% died after two years. Treatment with corticosteroids only added a little more than a year to overall survival.

Current treatment of GPA is immunosuppressive therapy, initially cyclophosphamide or rituximab and glucocorticoids to induce remission. Patients with severe renal or pulmonary involvement at presentation may also undergo plasma exchange in addition to supportive therapy. Most remissions occur in two to six months, and studies have shown percent remission rates in the high 80s to low 90s.

Once in remission, maintenance therapy with azathioprine, methotrexate or rituximab may be continued for 12 to 24 months to prevent relapse. Relapse rates after first remission vary widely, possibly due to differences in treatment, time to remission and even differences in definitions of relapse. Different studies report relapse rates of 14-40%. In patients who have had multiple relapses maintenance therapy may be continued indefinitely.

Continued

CASE #1

Granulomatosis with Polyangiitis

Cont.

While the mortality associated with GPA has improved greatly with recent therapy, it is still higher than the general population and the insured population. In a study of 273 patients with MPO and PR3 ANCA associated vasculitis in which 22% did not have renal involvement, the average age was 52 for those without renal involvement and 58 for those with renal involvement. They reported overall survival at 1, 5 and 10 years as 90%, 83% and 74%, respectively. They also found survival to be significantly better in those who were PR3 ANCA positive as opposed to MPO ANCA positive. Those patients with renal failure were at a significant survival disadvantage.

Another study of GPA compared to general population mortality found a Mortality Risk Ratio (MRR) of 3.8 (95% CI 2.6 to 5.6), MMR 4.0 for men (95% CI 2.5 to 6.3), MRR 3.4 for women (95% CI 1.6 to 7.2). Factors adversely affecting survival include older age and end organ damage (especially renal damage). Causes of death associated with GPA include infections, renal failure, pulmonary failure and cardiovascular disease.

There is also an increased risk of cancer with this disease. A study of the Swedish inpatient register linking Wegener's to cancer for up to 26 years found a two-fold overall increased risk for cancer in the cohort. The increase was most pronounced for bladder cancer (SIR 4.8; 95% CI 2.6–8.1), squamous cell skin cancer (SIR 7.3; 95% CI 4.4–12), leukemias (SIR 5.7; 95% CI 2.3–12) and for malignant lymphomas (SIR 4.2; 95% CI 4.2–8.3).

Returning to the case

Given the high rate of relapse of GPA it would be prudent to postpone for some time after the completion of treatment. When reconsidering, special attention should be paid to renal function, urinalysis and any end organ (lungs, heart) damage that may have occurred.

REFERENCES

DeJoode A et al, "Renal Survival in Proteinase 3 and Myeloperoxidase ANCA-Associated Systemic Vasculitis", Clin J Am Soc Nephrol 2013;8:1709–1717.

Mukhtyar C, et al. "Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force." Ann Rheum Dis 2008;67:1004–1010.

Knight A, et al, "Cancer Incidence in a Population-Based Cohort of Patientswith Wegener's Granulomatosis," Int. J. Cancer 2002;100:82–85.

Hogan J, et al, "Is Newer Safer? Adverse Events Associated with First-Line Therapies for ANCA-Associated Vasculitis and Lupus Nephritis," Clin J Am Soc Nephrol 2014;9:1657–1667.

Goceroglu A, et al, "ANCA-Associated Glomerulonephritis: Risk Factors for Renal Relapse," PLoS ONE 2016 11(12): e0165402, doi:10.1371/journal.pone.0165402

Up To Date: Last Accessed 3/1/2017.

CASE #2

Attention Deficit Hyperactivity Disorder

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A family is applying for life insurance for their 20-year-old college student daughter. The applied for amount, while high, appears consistent with siblings. The potential insured's (PI) attending physician statement (APS) has regular routine health maintenance checkups, with a few emergency room follow ups for injuries, including a forearm fracture at age 13 without specifics mentioned, a foot fracture from falling after trying to climb out of a second story bedroom window at the age of 15, and a follow up from a motor vehicle accident where the PI was a passenger at the age of 17 years.

The young lady was diagnosed with ADHD at the age of 7 and has been treated with stimulants since that time. She and her family have participated in family counseling on and off throughout the years. Her BMI and vital signs fall within normal limits. She is on no other medications except for methylphenidate.

1. Does ADHD present a mortality risk?
2. Are there any indicators that increase or decrease that risk?

Epidemiology

Attention Deficit Hyperactivity Disorder (ADHD) is an oft discussed and frequently diagnosed disorder. As of 2011, the CDC reports that approximately 11% of children aged 4-17 years of age have been diagnosed with ADHD. Approximately 4.1% of adults in the US also carry the same diagnosis. The average age at diagnosis is 7 years, and the male:female ratio is 2.6:1.

It appears that genetics plays a strong role, but other factors are being examined, including prematurity, exposures to toxins in utero (such as drugs or alcohol), brain injury, etc. Research does not support some popularly held views that family chaos, lack of discipline, lack of a full night of sleep, etc. are causes, although all can certainly contribute to worsening of symptoms.

Continued

CASE #2

Attention Deficit Hyperactivity Disorder

Cont.

Diagnosis

The diagnosis of ADHD in the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 now encompasses both ADHD and the former Attention Deficit Disorder (ADD). This change was made as it is believed that ADHD may look different at different stages of life. One can present with predominantly inattentive, predominantly hyperactive/impulsive or with combined features, yet the prevalent symptoms can change over time.

To receive the diagnosis, several inattentive or hyperactive-impulsive symptoms must be present before age 12 years; they must be present in two or more settings; and there must be clear evidence that the symptoms interfere with the quality of social, school or work functioning.

Inattention

Six or more of the following symptoms must be present for children up to age 16 years or five or more symptoms must be present for those 17 years or older. Symptoms must be present for more than six months and must be inappropriate for the developmental level of the individual.

A Often fails to give close attention to details or makes careless mistakes

B Often has trouble holding attention on tasks or play activities

C Often does not seem to listen when spoken to directly

D Often does not follow through on instructions and fails to finish tasks

E Often has trouble organizing tasks and activities

F Often avoids, dislikes or is reluctant to do tasks that require mental effort over a long period of time

G Often loses things necessary for tasks and activities

H Is often easily distracted

I Is often forgetful in daily activities

Hyperactivity and Impulsivity

Six or more of the following symptoms must be present for children up to age 16 years or five or more symptoms must be present for those 17 years or older. Symptoms must be present for more than six months and must be disruptive and inappropriate for the developmental level of the individual.

A Often fidgets with or taps hands or feet or squirms in seat

B Often leaves seat in situations when remaining seated is expected

C Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless)

D Often unable to play or take part in leisure activities quietly

E Is often "on the go" acting as if "driven by a motor"

F Often talks excessively

G Often blurts out an answer before a question has been completed

H Often has trouble waiting his/her turn

I Often interrupts or intrudes on others (e.g., butts into conversations or games)

American Academy of Pediatrics Recommendations

It is recommended by the American Academy of Pediatrics in their 2011 *ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/ Hyperactivity Disorder in Children and Adolescents Clinical Practice* that a primary care clinician should evaluate all children aged 4-18 years who present with academic or behavioral problems and symptoms of inattention, hyperactivity or impulsivity.

The evaluation should include assessing for any contributing or coexisting impairments such as emotional, behavioral, developmental or physical conditions.

If ADHD is diagnosed, the treatment should include age appropriate counseling and behavior therapy for both at home and school and stimulant medication if needed.

Continued

CASE #2

Attention Deficit Hyperactivity Disorder

Cont.

Pharmacotherapy

First line medications are stimulants (methylphenidate and amphetamine) and norepinephrine reuptake inhibitor (atomoxetine).

Second line medications are reserved for first line drug failures or unacceptable side effects and include alpha 2-adrenergic agonists (clonidine, guanfacine), antidepressants (tricyclic antidepressants and bupropion) and atypical antipsychotics (risperdone, ziprasidone, aripiprazole). Some of these medications (atypical antipsychotics) are used off label or when there are comorbidities such as autism spectrum disorder, agitation or aggression **(Table 1).**

Natural History

Barbaresi et al. Pediatrics 2013 examined the records of 5,718 children born in Minnesota between 1976-1982 and diagnosed with ADHD. The prospective portion of their study revealed that of all of the children who received the diagnosis of childhood ADHD, during adulthood, 5.6% had only adult ADHD, 23.7% had adult ADHD and a psychiatric disorder, 33.2% carried a diagnosis of only a psychiatric disorder, while 37.5% of the population had no diagnosed condition at all. It appears from these findings that some children outgrow the symptoms, while others have symptoms which evolve into another diagnostic category.

TABLE 1 – ADHD MEDICATIONS

Common	Secondary
Methylphenidate	**Alpha2-adrenergic agonists**
Ritalin	Clonidine/Catapres
Focalin	Guanfacine/Intuniv
Metadate	**Antidepressants**
Concerta	Tricyclic antidepressants
Daytrana Patch	Desipramine
Amphetamine	Nortiptyline
Dextroamphetamine	Bupropion/Wellbutrin
Vyvanse	**Atypical Antipsychotics**
Lisdexamfetamine	Risperidone/Risperdal
Atomoxetine/Strattera	Ziprasidone/Geodon
	Aripiprazole/Abilify

Mortality Implications

Dalsgaard et al in Lancet 2015 followed 1.92 million Danish individuals born 1981-2011, from first birthday until 2013, including 32,061 with ADHD. The adjusted mortality rate ratio is shown in Table 2.

There is a baseline elevation of mortality risk with ADHD alone. The addition of the comorbidities of Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) and/or Substance Use Disorder increase the mortality risk in a dose-response fashion.

When looking at the results broken down by gender, a higher relative mortality rate is realized by females **(Table 3)**.

This effect may be due to a combination of factors. Females are diagnosed with ADHD less frequently than males, and one might hypothesize that those girls who receive the ADHD diagnosis may have more severe and impairing symptoms. Girls also tend to receive pharmacotherapy less frequently than boys, which may also contribute to the difference.

The results of the study also determined that the increased mortality was driven by deaths from unnatural causes, most commonly accidents.

This fits with our understanding of the disorder where impulsivity often rules over caution.

TABLE 2 – ADJUSTED MORTALITY RATE RATIO

Diagnosis	Adjusted MRR
ADHD	1.50
ADHD + ODD or CD	2.17
ADHD + Substance Use Disorder	5.63
ADHD + ODD or CD + Substance Use Disorder	8.29
ODD or CD or Substance Use Disorder	3.55
`Control	1.00

ODD = Oppositional Defiant Disorder CD = Conduct Disorder
MMR = Mortality Rate Ratio

TABLE 3 - ADHD WITHOUT ODD, CD OR SUBSTANCE USE DISORDER, BROKEN DOWN BY GENDER

Gender	MRR
Male	1.27
Female	2.85

Returning to the Case

Our young applicant has been diagnosed with ADHD and is being treated pharmacologically with a first line medication. She does not, as far as we know, carry any comorbid diagnoses that increase mortality. She has been successfully treated for a few accidents which may or may not have been a direct result of her ADHD.

Given our current understanding of the ADHD and the recent mortality data, the case was assessed at mild to moderate excess mortality.

Postscript

Sections of SOLEM Americas Underwriting Guide on Hypertrophic and Dilated Cardiomyopathies have been updated. Addition of guidance, tables and calculators for Juvenile Build are currently in production. Look for these to be added by the end of the second quarter.

REFERENCES

Barbaresi, William J., Robert C. Colligan, Amy L. Weaver, Robert G. Voigt, Jill M. Killian, and Slavica K. Katusic. "Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study." Pediatrics 131, no. 4 (2013): 637-644.

Dalsgaard, Søren, Søren Dinesen Østergaard, James F. Leckman, Preben Bo Mortensen, and Marianne Giørtz Pedersen. "Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study." The Lancet 385, no. 9983 (2015): 2190-2196.

https://www.cdc.gov/ncbddd/adhd/data.html accessed 2/17/2017

UpToDateR last accessed 2/17/2017

EKG

Lab Puzzler...

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In this issue of the *Puzzler* Dr. Rooney presents a Lab Puzzler.

To find the answer, be sure to visit the Housecalls page on www.scorgloballifeamericas.com. Click on March 2017 Puzzler to confirm your findings.

A 28-year-old male applies for $1 million dollars of life insurance. He recently tried to donate blood but was declined because of an abnormal Hepatitis B test. The Hepatitis B core antibody was positive. LFT's were normal. HBsAg was negative.

Are there any mortality concerns from this situation?

EVENT CALENDAR

Where to Meet Us

As a leader in the US life reinsurance industry, SCOR is committed to sharing its knowledge and experience with the industry. In addition to volunteering time, service and expertise to industry associations, a key mission is to share our perspective at industry meetings through presentations and one-on-one meetings. Paolo De Martin participated in the CEO Roundtable at Refocus in March. Below is a list of upcoming industry events and SCOR employees scheduled to present. We look forward to seeing you at the upcoming meetings.

UPCOMING INDUSTRY MEETINGS

Meeting (Location, Date)	Session	SCOR Presenter
AHOU Annual Meeting (San Diego, April 2-5, 2017)	Evolution of Age/Amount Requirements	Cindy Mitchell
	The Pediatric Brain	Dr. Regina Rosace
	Mortality Trends	Philippe Aussel
GUAA Conf (Denver, May 21-14, 2017)	Drivers of Future Mortality: Why Aren't We Dead Yet?	Philippe Aussel

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