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Review Article

Current status of autoimmune diseases with special references to their possible therapies: A review

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Abstract

The healthy human body is equipped with a powerful set of tools for resisting the onslaught of invading microorganisms (such as viruses, bacteria, and parasites). Unfortunately, this set of tools, known as the immune system, sometimes goes awry and attacks the body itself. These misdirected immune responses are referred to as autoimmunity, which can be demonstrated by the presence of autoantibodies or T lymphocytes reactive with host antigens. The present paper deals with the various these aspects of autoimmune diseases and possible therapies and approaches.

Keywords: Auto-immune disease, Antibiotics, Antibodies, Antigen.

Introduction

Autoimmunity is present in everyone to some extent. It is usually harmless and probably a universal phenomenon of vertebrate life. However, autoimmunity can be the cause of a broad spectrum of human illnesses, known as autoimmune diseases. This concept of autoimmunity as the cause of human illness is relatively new, and it was not accepted into the mainstream of medical thinking until the 1950s and 1960s. Autoimmune diseases are, thus, defined when the progression from benign autoimmunity to pathogenic autoimmunity occurs. Both genetic influences and environmental triggers determine this progression. The concept of autoimmunity as the actual cause of human illness (rather than a consequence or harmless accompaniment) can be used to establish criteria that define a disease as an autoimmune disease. By this approach, Rose and Bona have distinguished the evidence for an autoimmune etiology at three different levels: direct, indirect, and circumstantial[1-4].

Direct evidence requires transmissibility of the characteristic lesions of the disease from human to human or human to animal. In the real world, such evidence is attainable at this time only for diseases mediated by autoantibody, since we do not yet have the means for reliably studying T lymphocyte-mediated autoimmune diseases by transfer to animals.

Examples of autoimmune diseases that fulfill the criteria of direct evidence are idiopathic thrombocytopenic purpura (in which deliberate human experimentation in the early 1950s showed that the platelet Destruction is directly caused by an autoantibody), Graves' disease and myasthenia gravis (in which there are temporary signs of disease in the infant due to transplacental transfer), pemphigus vulgaris and bullous pemphigoid (where the disease can be transmitted from humans to animals by autoantibody). Another, more feasible, way to demonstrate pathologic effect of autoantibody is to reproduce the functional defects characteristic of the disease in vitro. For example, inhibition of the fixation of vitamin B12 by intrinsic factor can be produced by autoantibodies from certain patients with pernicious anemia, and overproduction of thyroid hormones can be produced by autoantibodies from patients with Graves' disease. Indirect evidence requires re-creation of the human disease in an animal model. The majority of autoimmune diseases fit in this category. For example, the autoimmune basis of systemic lupus erythematosus is well accepted because of the availability of several genetically determined mouse models which, while not simulating lupus as seen in the clinic, do very closely replicate the serological features and some pathological features. Hashimoto's thyroiditis and multiple sclerosis can be reproduced by immunizing the animal with an antigen analogous to the putative autoantigen of the human disease. The development of animal models is increasing rapidly as methods of genetic and immunologic manipulation become commonplace. For example, knock-out mice have provided the best models of inflammatory bowel disease; neonatal thymectomy of mice can produce excellent analogs of human oophoritis and autoimmune gastritis. It is worth noting that animal models must be viewed with caution as being an analog rather than the exact copy of the human counterpart, because they invariably differ to some degree from the human disease[2-8].

When direct and indirect evidence to define an autoimmune disease are not available, investigators are left with circumstantial evidence, that is, with listing "markers" descriptive of autoimmune disease. Examples of these markers are:

- Positive family history for the same disease, or for other diseases known to be autoimmune
- Presence in the same patient of other known autoimmune diseases
- Presence of infiltrating mononuclear cells in the affected organ or tissue
- Preferential usage of certain MHC class II allele
- High serum levels of IgG autoantibodies
- Deposition of antigen-antibody complexes in the affected organ or tissue
- Improvement of symptom with the use of immunosuppressive drugs (such as corticosteroids)

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joints producing a inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most common in subcutaneous tissue under the skin. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in its chronicity and progression.

Signs and symptoms

While rheumatoid arthritis primarily affects joints, problems involving other organs of the body are known to occur. Extra-articular ("outside the joints") manifestations other than anemia (which is very common) are clinically evident in about 15-25% of individuals with rheumatoid arthritis. It can be difficult to determine whether disease manifestations are directly caused by the rheumatoid process itself, or from side effects of the medications commonly used to treat it - for example, lung fibrosis from methotrexate, or osteoporosis from corticosteroids.

Joints

The arthritis of rheumatoid arthritis is due to synovitis, which is inflammation of the synovial membrane that lines joints and tendon sheaths. Joints become swollen, tender and warm, and stiffness limits their movement. With time, RA nearly always affects multiple joints (it is a polyarthritis). Most commonly, small joints of the hands, feet and

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Table 1: Types of AutoImmune Disease[5-10]

Human Autoimmune Diseases			
Disease	**Autoantigen**	**Symptoms**	**Extent***
Type II: antibodies to cell surface molecules			
Autoimmune hemolytic anemia	Rh blood group antigens, I antigen	Lysis of RBC by complement and FcR^+ cells, anemia	O
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding	O
Goodpasture's syndrome	Basement membrane Type IV collagen	Glomerulonephritis, pulmonary hemorrhage	O
Graves' disease	Thyroid-stimulating hormone receptor	Thyroid over-activity	O
Hashimoto's thyroiditis	Thyroglobulin, thyroid peroxidase	Thyroid under-activity	O
Hypoglycemia	Insulin receptor (agonist)	Low blood glucose	O
Insulin-resistant diabetes	Insulin receptor (antagonist)	High blood glucose, ketoacidosis	O
Pemphigus vulgaris	Epidermal cadherin	Skin blisters	O
Pernicious anemia	Intrinsic factor, gastric parietal cells	Anemia	O
Rheumatic fever	Streptococcal cell wall antigens; antibodies cross-react with heart muscle	Arthritis, myocarditis, heart valve scars	O
Spontaneous infertility	Sperm antigens	Infertility	O
Type III: Immune complex disease			
Ankylosing spondylitis	Immune complexes	Damage to vertebrae	S
Mixed essential cryoglobulinemia	Rheumatoid factor IgG complexes	Systemic vasculitis	S
Rheumatoid arthritis	Rheumatoid factor IgG complexes	Arthritis	S
Systemic lupus erythematosus (**SLE**)	DNA, histones, ribosomes, snRNP, scRNP	Glomerulonephritis, vasculitis, rash	S
Type IV: T cell-mediated disease			
Experimental autoimmune encephalomyelitis (**EAE**), multiple sclerosis (**MS**)	Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein	Brain invasion by CD4 T cells, weakness	S
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction	S

*O = organ-specific, S = system

cervical spine are affected, but larger joints like the shoulder and knee can also be involved, differing per individual. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface, causing deformity and loss of function.

Rheumatoid arthritis typically manifests with signs of inflammation, and the affected joints are swollen, warm, painful and stiff early in the morning on waking, or following prolonged inactivity. Increased stiffness early in the morning is often a prominent feature of the inflammatory disease which the person may experience and may last for more than an hour. Gentle movements may relieve symptoms in early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, often referred to as osteoarthritis or "wear-and-tear" arthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are absent and also movements aggravate pain due to the wear-and-tear. In RA, the joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical.

Lungs

Fibrosis of the lungs is a recognised response to rheumatoid disease. It is also a rare but well recognised consequence of therapy (for example with methotrexate and leflunomide). Caplan's syndrome describes lung nodules in individuals with rheumatoid arthritis and additional exposure to coal dust. Pleural effusions are also associated with rheumatoid arthritis.

Kidneys

Renal amyloidosis can occur as a consequence of chronic inflammation. Rheumatoid arthritis may affect the kidney glomerulus directly through a vasculopathy or a mesangial infiltrate but this is less well documented. Treatment with Penicillamine and gold salts are recognized causes of membranous nephropathy.

Heart and blood vessels

People with rheumatoid arthritis are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and stroke is markedly increased. Other possible complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis.

Treatment

There is no known cure for rheumatoid arthritis, but many different types of treatment can alleviate symptoms and/or modify the disease process. The goal of treatment is two-fold: alleviating the current symptoms, and preventing the future destruction of the joints with the resulting handicap if the disease is left unchecked. These two goals may not always coincide: while pain relievers may achieve the first goal, they do not have any impact on the long-term consequences. For these reasons, most authorities believe that most RA should be treated by at least one specific anti-rheumatic medication, also named DMARD, to which other medications and non-medical interventions can be added as needed.

Disease modifying anti-rheumatic drugs (DMARDS)

The term Disease modifying anti-rheumatic drug (DMARD) originally meant a drug that affects biological measures such as ESR and haemoglobin and autoantibody levels, but is now usually used to mean a drug that reduces the rate of damage to bone and cartilage. DMARDs have been found both to produce durable symptomatic remissions and to delay or halt progression. This is important as such damage is usually irreversible. Anti-inflammatories and analgesics improve pain and stiffness but do not prevent joint damage or slow the disease progression.

There is an increasing recognition among rheumatologists that permanent damage to the joints occurs at a very early stage in the disease. In the past it was common to start with just an anti-inflammatory drug, and assess progression clinically and using X-rays. If there was evidence that joint damage was starting to occur then a more potent DMARD would be prescribed. Ultrasound and MRI are more sensitive methods of imaging the joints and have demonstrated that joint damage occurs much earlier and in more sufferers than was previously thought. People with normal X-rays will often have erosions detectable by ultrasound that X ray could not demonstrate. The aim now is to treat before damage occurs.

Delaying therapy for as little as a few months after the onset of symptoms can result in worse outcomes in the long term. There is therefore considerable interest in establishing the most effective therapy with early arthritis, when they are most responsive to therapy and have the most to gain.

Traditional small molecular mass drugs

- azathioprine
- ciclosporin (cyclosporine A)
- D-penicillamine
- gold salts
- hydroxychloroquine
- leflunomide
- methotrexate (MTX)
- minocycline
- sulfasalazine (SSZ)

The most important and most common adverse events relate to liver and bone marrow toxicity (MTX, SSZ, leflunomide, azathioprine, gold compounds, D-penicillamine), renal toxicity (cyclosporine A, parenteral gold salts, D-penicillamine), pneumonitis (MTX), allergic skin reactions (gold compounds, SSZ), autoimmunity (D-penicillamine, SSZ, minocycline) and infections (azathioprine, cyclosporine A). Hydroxychloroquine may cause ocular toxicity, although this is rare, and because hydroxychloroquine does not affect the bone marrow or liver it is often considered to be the DMARD with the least toxicity. Unfortunately hydroxychloroquine is not very potent, and is usually insufficient to control symptoms on its own.

Many rheumatologists consider methotrexate to be the most important and useful DMARD, largely because of lower drop-out rates for reasons of toxicity. Nevertheless, methotrexate is often considered as a very 'toxic' drug. This reputation is not entirely justified, and at times can result in people being denied the most effective treatment for their arthritis. Although methotrexate does have the potential to suppress bone marrow or cause hepatitis, these effects can be monitored using regular blood tests, and the drug withdrawn at an early stage if the tests are abnormal before any serious harm is done (typically the blood tests return to normal after stopping the drug). In clinical trials, where one of a range of different DMARDs were used, people who were prescribed methotrexate stayed on their medication the longest (the others stopped because of either side-effects or failure of the drug to control the arthritis). Methotrexate is often preferred by rheumatologists because if it does not control arthritis on its own then it works well in combination with many other drugs, especially the biological agents. Other DMARDs may not be as effective or as safe in combination with biological agents.

Biological Agents

Biological agents (biologics) are produced through genetic engineering, and include:

- tumor necrosis factor alpha (TNFα) blockers - etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira)
- Interleukin 1 (IL-1) blockers - anakinra (Kineret)
- monoclonal antibodies against B cells - rituximab (Rituxan)
- T cell costimulation blocker - abatacept (Orencia)
- Interleukin 6 (IL-6) blockers - tocilizumab (an anti-IL-6 receptor antibody) (RoActemra, Actemra)

Anti-Inflammatory Agents and Analgesics

Anti-inflammatory agents include:

- glucocorticoids
- Non-steroidal anti-inflammatory drug (NSAIDs, most also act as analgesics)

Analgesics include:

- paracetamol (acetaminophen in US and Canada!)
- opiates
- diproqualone
- lidocaine topical

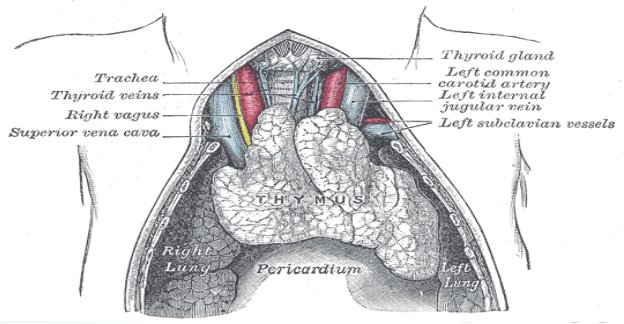
Historic treatments for RA have also included: rest, ice ,compression and elevation, acupuncture, apple diet, nutmeg, some light exercise every now and then, nettles, bee venom, copper bracelets, rhubarb diet, rest, extractions of teeth, fasting, honey, vitamins, insulin, magnets, and electroconvulsive therapy (ECT). Most of these have either had no effect at all, or their effects have been modest and transient, while not being generalizable.

Other Therapies

Other therapies are weight loss, occupational therapy, podiatry, physiotherapy, immunoadsorbtion therapy, joint injections, and special tools to improve hard movements (e.g. special tin-openers). Regular exercise is important for maintaining joint mobility and making the joint muscles stronger. Swimming is especially good, as it allows for exercise with a minimum of stress on the joints. Heat and cold applications are modalities that can ease symptoms before and after exercise. Pain in the joints is sometimes alleviated by oral ibuprofen or other anti-inflammatory. Other areas of the body, such as the eyes and.

Mysthenia gravis

Myasthenia gravis (literally "serious muscle-weakness"; from Greek "muscle", "weakness", and Latin gravis "serious"; abbreviated MG) is a neuromuscular disease leading to fluctuating muscle weakness and fatiguability. It is an autoimmune disorder, in which weakness is caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction,inhibiting the stimulative effect of the neurotransmitter acetylcholine. Myasthenia is treated medically with cholinesterase inhibitors or immunosuppressants, and, in selected cases, thymectomy. At 200–400 cases per million it is one of the less common autoimmune disorders.



Myasthenia gravis is a chronic autoimmune neuromuscular disease characterized by varying degrees of weakness of the skeletal (voluntary) muscles of the body. The name myasthenia gravis, which is Latin and Greek in origin, literally means "grave muscle weakness." With current therapies, however, most cases of myasthenia gravis are not as "grave" as the name implies. In fact, for the majority of individuals with myasthenia gravis, life expectancy is not lessened by the disorder.

Classification[8-17]

The most widely accepted classification of myasthenia gravis is the Myasthenia Gravis Foundation of America Clinical Classification:

Class I: Any eye muscle weakness, possible apoptosis, no other evidence of muscle weakness elsewhere

Class II: Eye muscle weakness of any severity, mild weakness of other muscles

Class IIa: Predominantly limb or axial muscles

Class IIb: Predominantly bulbar and/or respiratory muscles

Class III: Eye muscle weakness of any severity Moderate weakness of other muscles

Class IIIa: Predominantly limb or axial muscles

Class IIIb: Predominantly bulbar and/or respiratory muscles

Class IV: Eye muscle weakness of any severity, severe weakness of other muscles

Class IVa: Predominantly limb or axial muscles

Class IVb: Predominantly bulbar and/or respiratory muscles (Can also include feeding tube without intubation)

Class V: Intubation needed to maintain airway

Signs and Symptoms

The hallmark of myasthenia gravis is fatiguability. Muscles become progressively weaker during periods of activity and improve after periods of rest. Muscles that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are especially susceptible. The muscles that control breathing and neck and limb movements can

also be affected. Often the physical examination is within normal limits. The onset of the disorder can be sudden. Often symptoms are intermittent. In most cases, the first noticeable symptom is weakness of the eye muscles. In others, difficulty in swallowing and slurred speech may be the first signs. The degree of muscle weakness involved in MG varies greatly among patients, ranging from a localized form, limited to eye muscles (ocular myasthenia), to a severe or generalized form in which many muscles - sometimes including those that control breathing - are affected. Symptoms, which vary in type and severity, may include asymmetrical apoptosis (a drooping of one or both eyelids), diplopia (double vision) due to weakness of the muscles that control eye movements, unstable or waddling gait, weakness in arms, hands, fingers, legs, and neck, a change in facial expression, dysphagia (difficulty in swallowing), shortness of breath and dysarthria (impaired speech, often nasal due to weakness of the velar muscles). In myasthenic crisis a paralysis of the respiratory muscles occurs, necessitating assisted ventilation to sustain life. In patients whose respiratory muscles are already weak, crises may be triggered by infection, fever, an adverse reaction to medication, or emotional stress. Since the heart muscle is stimulated differently, it is never affected by MG.

Treatment

Treatment is by medication and/or surgery. Medication consists mainly of cholinesterase inhibitors to directly improve muscle function and immunosuppressant drugs to reduce the autoimmune process. Thymectomy is a surgical method to treat MG. For emergency treatment, plasmapheresis or IVIG can be used as a temporary measure to remove antibodies from the blood circulation. Acetylcholinesterase inhibitors: neostigmine and pyridostigmine can improve muscle function by slowing the natural enzyme cholinesterase that degrades acetylcholine in the motor end plate. Immunosuppressive drugs: prednisone, cyclosporine, mycophenolate mofetil and azathioprine may be used. It is common for patients to be treated with a combination of these drugs with a cholinesterase inhibitor. Treatments with some immunosuppressives take weeks to months before effects are noticed. Other immunomodulating substances, like drugs preventing acetylcholine receptor modulation by the immune system are currently being researched.

Diabetes mellitus

Diabetes mellitus often referred to simply as diabetes (Ancient Greek: "to pass through"), is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the beta cells of the pancreas. Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action in the body. Diabetes develops due to a diminished production of insulin (in *type 1*) or resistance to its effects (in *type 2* and *gestational*). Both lead to hyperglycemia, which largely causes the acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism.

Diabetes and its treatments can cause many complications. Acute complications (hypoglycemia, ketoacidosis, or nonketotic hyperosmolar coma) may occur if the disease is not adequately controlled. Serious long-term complications include cardiovascular disease (doubled risk), chronic renal failure, retinal damage (which can lead to blindness), nerve damage (of several kinds), and microvascular damage, which may cause erectile dysfunction and poor wound healing. Poor healing of wounds, particularly of the feet, can lead to gangrene, and possibly to amputation. Adequate treatment of diabetes, as well as increased emphasis on blood pressure control and lifestyle factors (such as not smoking and maintaining a healthy body weight), may improve the risk profile of most of the chronic complications. In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly and the leading cause of non-traumatic amputation in adults, and diabetic nephropathy is the main illness requiring renal dialysis in the United States.

Diabetes mellitus is a condition in which the pancreas no longer produces enough insulin or when cells stop responding to the insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body. Symptoms include frequent urination, lethargy, excessive thirst, and hunger. The treatment includes changes in diet, oral medications, and in some cases, daily injections of insulin

Classification

Type 1 Diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to a deficiency of insulin. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated variety, where beta cell loss is a T-cell mediated autoimmune attack .There is no known preventive measure which can be taken against type 1 diabetes; it is about 10% of diabetes mellitus cases in North America and Europe (though this varies by geographical location), and is a higher percentage in some other areas. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children. The principal treatment of type 1 diabetes, even in its earliest stages, is the delivery of artificial insulin via injection combined with careful monitoring of blood glucose levels using blood testing monitors. Without insulin, diabetic ketoacidosis often develops which may result in coma or death. Treatment emphasis is now also placed on lifestyle adjustments (diet and exercise) though these cannot reverse the progress of the disease. Apart from the common subcutaneous injections, it is also possible to deliver insulin by a pump, which allows continuous infusion of insulin 24 hours a day at preset levels, and the ability to program doses (a bolus) of insulin as needed at mealtimes.

Type 2 Diabetes

Type 2 diabetes mellitus is characterized differently and is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion which in some cases becomes absolute. The defective responsiveness of body tissues to insulin almost certainly involves the insulin receptor in cell membranes. However, the specific defects are not known. Diabetes mellitus due to a known specific defect are classified separately. Type 2 diabetes is the most common type.

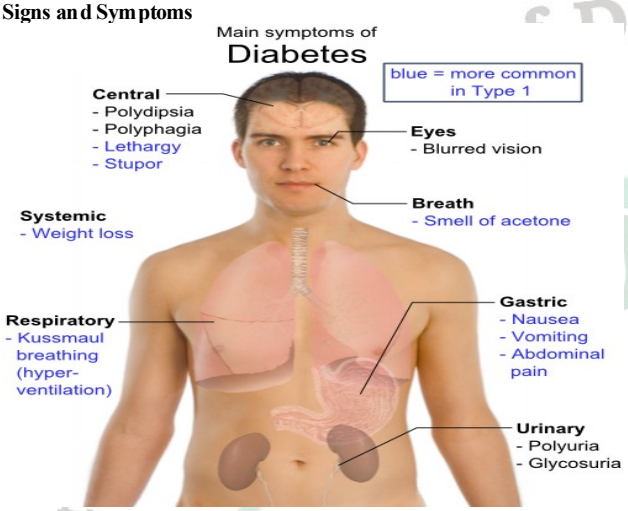
In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood. At this stage hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. As the disease progresses, the impairment of insulin secretion worsens, and therapeutic replacement of insulin often becomes necessary. There are numerous theories as to the exact cause and mechanism in type 2 diabetes. Central obesity (fat concentrated around the waist in relation to abdominal organs, but not subcutaneous fat) is known to predispose individuals to insulin resistance. Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines that may possibly impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes. Other factors include aging (about 20% of elderly patients in North America have diabetes) and family history (type 2 is much more common in those with close relatives who have had it). In the last decade, type 2 diabetes has increasingly begun to affect children and adolescents, likely in connection with the increased prevalence of childhood obesity seen in recent decades in some places. Environmental exposures may contribute to recent increases in the rate of type 2 diabetes. A positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of polycarbonate plastic, and the incidence of type 2 diabetes.

Type 2 diabetes may go unnoticed for years because visible symptoms are typically mild, non-existent or sporadic, and usually there are no ketoacidotic episodes. However, severe long-term complications can result from unnoticed type 2 diabetes, including renal failure due to diabetic nephropathy, vascular disease (including coronary artery disease), vision damage due to diabetic retinopathy, loss of sensation or pain due to diabetic neuropathy, liver damage from non-alcoholic steatohepatitis and heart failure from diabetic cardiomyopathy.

Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Signs and Symptoms



The classical triad of diabetes symptoms is polyuria, polydipsia and polyphagia, which are, respectively, frequent urination, increased thirst and consequent increased fluid intake, and increased appetite. Symptoms may develop quite rapidly (weeks or months) in type 1 diabetes, particularly in children. However, in type 2 diabetes symptoms usually develop much more slowly and may be subtle or completely absent. Type 1 diabetes may also cause a rapid yet significant weight loss (despite normal or even increased eating) and irreducible mental fatigue. All of these symptoms except weight loss can also manifest in type 2 diabetes in patients whose diabetes is poorly controlled.

When the glucose concentration in the blood is raised beyond its renal threshold, reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst.

Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eyes, resulting in vision changes; sustained sensible glucose control usually returns the lens to its original shape. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change, whereas with type 2 change is generally more gradual, but should still be suspected. Patients (usually with type 1 diabetes) may also initially present with diabetic ketoacidosis (DKA), an extreme state of metabolic dysregulation characterized by the smell of acetone on the patient's breath; a rapid, deep breathing known as Kussmaul breathing; polyuria; nausea; vomiting and abdominal pain; and any of many altered states of consciousness or arousal (such as hostility and mania or, equally, confusion and lethargy). In severe DKA, coma may follow, progressing to death. Diabetic ketoacidosis is a medical emergency and requires immediate hospitalization.

Treatment and Management

Diabetes mellitus is currently a chronic disease, without a cure, and medical emphasis must necessarily be on managing/avoiding possible short-term as well as long-term diabetes-related problems. There is an exceptionally important role for patient education, dietetic support, sensible exercise, self monitoring of blood glucose, with the goal of keeping both short-term blood glucose levels, and long term levels as well, within acceptable bounds. Careful control is needed to reduce the risk of long term complications. This is theoretically achievable with combinations of diet, exercise and weight loss (type 2), various oral diabetic drugs (type 2 only), and insulin use (type 1 and for type 2 not responding to oral medications, mostly those with extended duration diabetes). In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications should be undertaken to control blood pressure and cholesterol by exercising more, smoking less or ideally not at all, consuming an appropriate diet, wearing diabetic socks, wearing diabetic shoes, and if necessary, taking any of several drugs to reduce blood pressure.

Multiple sclerosis

Multiple sclerosis (abbreviated MS, also known as disseminated sclerosis or encephalomyelitis disseminata) is an autoimmune condition in which the immune system attacks the central nervous system, leading to demyelination. Disease onset usually occurs in young adults, and it is more common in females. It has a prevalence that ranges between 2 and 150 per 100,000. MS was first described in 1868 by Jean-Martin Charcot.

MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other. Nerve cells communicate by sending electrical signals called action potentials down long fibers called axons, which are wrapped in an insulating substance called myelin. In MS, the body's own immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals. The name multiple sclerosis refers to scars (scleroses – better known as plaques or lesions) in the white matter of the brain and spinal cord, which is mainly composed of myelin. Although much is known about the mechanisms involved in the disease process, the cause remains unknown. Theories include genetics or infections. Different environmental risk factors have also been found.

Almost any neurological symptom can appear with the disease, and often progresses to physical and cognitive disability. MS takes several forms, with new symptoms occurring either in discrete attacks (relapsing forms) or slowly accumulating over time (progressive forms). Between attacks, symptoms may go away completely, but permanent neurological problems often occur, especially as the disease advances.

There is no known cure for MS. Treatments attempt to return function after an attack, prevent new attacks, and prevent disability. MS medications can have adverse effects or be poorly tolerated, and many patients pursue alternative treatments, despite the lack of supporting scientific study. The prognosis is difficult to predict; it depends on the subtype of the disease, the individual patient's disease characteristics, the initial symptoms and the degree of disability the person experiences as time advances. Life expectancy of patients is nearly the same as that of the unaffected population.

Multiple sclerosis (MS) is a chronic autoimmune disorder affecting movement, sensation, and bodily functions. It is caused by destruction of the myelin insulation covering nerve fibers (neurons) in the central nervous system (brain and spinal cord).

Signs and Symptoms

Symptoms of MS usually appear in episodic acute periods of worsening (relapses, exacerbations, bouts or attacks), in a gradually-progressive deterioration of neurologic function, or in a combination of both.

The most common presentation of MS is the clinically isolated syndrome (CIS). In CIS, a patient has an attack suggestive of demyelination, but does not fulfill the criteria for multiple sclerosis. Only 30 to 70% of persons experiencing CIS later develop MS. The disease usually presents with sensorial (46% of cases), visual (33%), cerebellar (30%) and motor (26%) symptoms .Many rare initial symptoms have also been reported, including aphasia, psychosis and epilepsy. Patients first seeking medical attention commonly present with multiple symptoms. The initial signs and symptoms of MS are often transient, mild, and self-limited. These signs and symptoms often do not prompt a person to seek medical attention and are sometimes identified only retrospectively once the diagnosis of MS has been made. Cases of MS

are sometimes incidentally identified during neurological examinations performed for other causes. Such cases are referred to as *subclinical MS*.

The person with MS can suffer almost any neurological symptom or sign, including changes in sensation (hypoesthesia and paraesthesia),

muscle weakness, muscle spasms, or difficulty in moving; difficulties with coordination and balance (ataxia); problems in speech (dysarthria) or swallowing (dysphagia),visual problems (nystagmus, optic neuritis, or diplopia),fatigue, acute or chronic pain,and bladder and bowel difficulties. Cognitive impairment of varying degrees and emotional symptoms of depression or unstable mood are also common. The main clinical measure of disability progression and symptom severity is the Expanded Disability Status Scale or EDSS.

Multiple sclerosis relapses are often unpredictable, occurring without warning and without obvious inciting factors. Some attacks, however, are preceded by common triggers. Relapses occur more frequently during spring and summer. Infections such as the common cold, influenza, or gastroenteritis increase the risk of relapse. Stress may also trigger an attack. Pregnancy may affect susceptibility to relapse, offering protection during the last trimester, for instance. During the first few months after delivery, however, the risk of relapse is increased. Overall, pregnancy does not seem to influence long-term disability. Many potential triggers have been examined and found not to influence MS relapse rates. There is no evidence that vaccination for influenza, hepatitis B, varicella, tetanus, or tuberculosis increases risk of relapse. Physical trauma does not trigger relapses. Exposure to higher than usual ambient temperatures can exacerbate extant symptoms, an effect known as Uhthoff's phenomenon. Uhthoff's phenomenon is not, however, an established relapse trigger.

Disease Subtypes

Several subtypes, or patterns of progression, have been described. Subtypes use the past course of the disease in an attempt to predict the future course. They are important not only for prognosis but also for therapeutic decisions. In 1996 the United States National Multiple Sclerosis Society standardized four subtype definitions: relapsing remitting, secondary progressive, primary progressive and progressive relapsing.

The relapsing-remitting subtype is characterized by unpredictable relapses followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. Deficits suffered during attacks may either resolve or leave sequelae. This describes the initial course of 85–90% of individuals with MS. When deficits always resolve between attacks, this is sometimes referred to as benign MS.

Secondary progressive MS describes those with initial relapsing-remitting MS, who then begin to have progressive neurologic decline between acute attacks without any definite periods of remission. Occasional relapses and minor remissions may appear. The median time between disease onset and conversion from relapsing-remitting to secondary progressive MS is 19 years.

The primary progressive subtype describes the approximately 10–15% of individuals who never have remission after their initial MS symptoms. It is characterized by progression of disability from onset, with no, or only occasional and minor, remissions and improvements.The age of onset for the primary progressive subtype is later than other subtypes.

Progressive relapsing MS describes those individuals who, from onset, have a steady neurologic decline but also suffer clear superimposed attacks. This isthe least common of all subtypes.

Cases with non-standard behavior have also been described. Sometimes referred to as borderline forms of multiple sclerosis, these include Devic's disease, Balo concentric sclerosis, Schilder's diffuse sclerosis and Marburg multiple sclerosis. Multiple sclerosis also behaves differently in children. There is debate whether these are atypical variants of MS or different diseases .

Diagnosis

T1-weighted MRI scans (post-contrast) of the same brain slice at monthly intervals. Bright spots indicate active lesions.

Multiple sclerosis can be difficult to diagnose since its signs and symptoms may be similar to many other medical problems. Medical organizations have created diagnostic criteria to ease and standardize the diagnostic process for practicing physicians. Historically, the Schumacher and Poser criteria were both popular. Currently, the McDonald criteria focus on a demonstration with clinical, laboratory and radiologic data of the dissemination of MS lesions in time and space. A diagnosis cannot be made until other possible conditions have been ruled out and there is evidence of demyelinating events separated anatomically and in time.

Clinical data alone may be sufficient for a diagnosis of MS if an individual has suffered separate episodes of neurologic symptoms characteristic of MS. Since some people seek medical attention after only one attack, other testing may hasten and ease the diagnosis. The most commonly used diagnostic tools are neuroimaging, analysis of cerebrospinal fluid and evoked potentials. Magnetic resonance imaging of the brain and spine shows areas of demyelination (lesions or plaques). Gadolinium can be administered intravenously as a contrast to highlight active plaques and, by elimination, demonstrate the existence of historical lesions not associated with symptoms at the moment of the evaluation. Testing of cerebrospinal fluid obtained from a lumbar puncture can provide evidence of chronic inflammation of the central nervous system. The cerebrospinal fluid is tested for oligoclonal bands, which are an inflammation marker found in 75–85% of people with MS. The nervous system of a person with MS often responds less actively to stimulation of the optic nerve and sensory nerves due to demyelination of such pathways. These brain responses can be examined using visual and sensory evoked potentials.

Treatment

Although there is no known cure for multiple sclerosis, several therapies have proven helpful. The primary aims of therapy are returning function after an attack, preventing new attacks, and preventing disability. As with any medical treatment, medications used in the management of MS have several adverse effects. Alternative treatments are pursued by some patients, despite the shortage of supporting, comparable, replicated scientific study.

Management of Acute Attacks

During symptomatic attacks, administration of high doses of intravenous corticosteroids, such as methylprednisolone, is the routine therapy for acute relapses. The aim of this kind of treatment is to end the attack sooner and leave fewer lasting deficits in the patient. Although generally effective in the short term for relieving symptoms, corticosteroid treatments do not appear to have a significant impact on long-term recovery. Potential side effects include osteoporosis and impaired memory, the latter being reversible.

Disease-modifying treatments

Disease-modifying treatments are expensive and most of these require frequent (up-to-daily) injections. Others require IV infusions at 1–3 month intervals.

The earliest clinical presentation of relapsing-remitting MS (RRMS) is the clinically isolated syndrome (CIS). Several studies have shown that treatment with interferons during an initial attack can decrease the chance that a patient will develop clinical MS.

The interferons and glatiramer acetate are delivered by frequent injections, varying from once-per-day for glatiramer acetate to once-per-week (but intra-muscular) for *Avonex*. Natalizumab and mitoxantrone are given by IV infusion at monthly intervals.

Treatment of progressive MS is more difficult than relapsing-remitting MS. Mitoxantrone has shown positive effects in patients with secondary progressive and progressive relapsing courses. It is moderately effective in reducing the progression of the disease and the frequency of relapses in patients in short-term follow-up.No treatment has been proven to modify the course of primary progressive MS.

Management of the effects of MS

Disease-modifying treatments reduce the progression rate of the disease, but do not stop it. As multiple sclerosis progresses, the symptomatology tends to increase. The disease is associated with a variety of symptoms and functional deficits that result in a range of progressive impairments and disability. Management of these deficits is therefore very important. Both drug therapy and neurorehabilitation have shown to ease the burden of some symptoms, though neither influences disease progression. As for any patient with neurologic deficits, a multidisciplinary approach is key to limiting and overcoming disability; however, there are particular difficulties in specifying a 'core team'

because people with MS may need help from almost any health profession or service at some point. Similarly, for each symptom there

are different treatment options. Treatments should therefore be individualized depending both on the patient and the physician.

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