INTRODUCTION

Long term hydroxychloroquine (HCQ) therapy has become a mainstay in the treatment of several chronic autoimmune diseases including systemic lupus Erythematosus (SLE), Juvenile rheumatoid arthritis (JRA). The drug was chosen for this role to replace its congener Chloroquine (CQ), in part, to avoid the retinotoxicity that developed with the use of this earlier treatment ***(Findbloom et al., 1985)***.

Although HCQ also was found to cause retinal damage, it appeared to do so at a much lower rate and was deemed safe for long term use ***(Bernstein, 1991)***. Despite occasional reports of retinal damage in a few patients, HCQ retinal toxicity is still considered by many to be a rare event ***(Marmor, 2005).***

The most common tests to detect HCQ toxicity have been visual acuity, visual fields (Amsler grid, Automated visual field), color vision testing, full-field electro-retinography (ERG), and multifocal electroretinography (mfERG) ***(Easterbrook, 1999).***

Because of the localized nature of the defects, mfERG seems to be better than the full-field ERG in detecting early retinal toxicity ***(Maturi et al., 2004).***

AIM OF THE WORK

Early detection of hydroxychloroquine retinal toxicity using multifocal electroretinography (mfERG) in children with systemic lupus erythematosus or juvenile rheumatoid arthritis.

CONNECTIVE TISSUE DISEASES IN PAEDIATRICS

Connective tissue diseases (rheumatic diseases) result from autoimmune process that leads to inflammation of target organs. Because many different organs may be affected, rheumatic diseases must be considered for a wide range of presenting complaints. Rarely, children develop overlap syndromes with manifestations fulfilling criteria for more than one rheumatic disease.

Early diagnosis of rheumatic disease may not always possible because specific diagnostic manifestations may take months or, rarely, even years to develop after initial presentation. Interval repeated clinical evaluations and review of the differential diagnosis is necessary in these circumstances ***(Miller, 2008).***

Atiology and pathogenesis

Rheumatic diseases are characterized by autoimmune responses. The immune system normally responds to viruses, bacteria, and other non-self molecules but does not mount reactions to self molecules. This property of tolerance to self is lost in rheumatic diseases. Two possible explanations, which are not mutually exclusive, for self-reactivity are:

1. Similarity between foreign and self molecules that are recognized by immune cells, particularly T lymphocytes.

2. Viral or other infections that incite, exaggerate, or prolong otherwise self-limited immune responses. Certain genetic factors such as, specific HLA alleles, may influence susceptibility to developing disease, whereas other factors such as, those that influence levels of baseline immune activities, may affect disease severity ***(Villanueva et al., 2005).***

Many rheumatic diseases are characterized by a serious of abnormal cellular and molecular events. T lymphocytes recognize viruses and other foreign antigens that rest in the groove of the HLA molecule on the surface of antigen-presenting cells. Molecular signals are released that activate other cells such as, macrophages, which produce inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), and IL-6 ***(Genovese et al., 2005).***

These cytokines cause tissue damage through direct effects and by attracting additional inflammatory cells to the affected site. Further tissue damage is sometimes mediated by B lymphocytes that are activated by helper T cells to produce excessive antibody, including autoantibodies that bind to self antigens. Normal cells in target organs can be destroyed by complement-mediated cytolysis, direct or indirect effects of

TNF-α, or effects of natural killer or cytolytic T lymphocytes ***(Ravelli et al., 2005).***

The autoimmune response may affect the function of many organs. For example, IL-6 and other cytokines bind to neuronal receptors in the central nervous system, causing fever, and can also interfere with osteoblastic activity, resulting in osteopenia. Molecules produced outside the immune system may, in turn, have an effect on immune responses ***(Burt et al., 2006).***

During a normal immune response, cytokines appear to induce neuroendocrine pathways to produce cortisol, which suppresses cellular and humoral immunity. It is possible that defects in these pathways amplify autoimmune responses. The increased incidence of some rheumatic diseases in females may be attributable to the property of female sex hormones to augment cellular immune responses ***(Ravelli and Martini, 2007).***

Clinical manifestations

A complete history is important to help distinguish rheumatic conditions from other diseases. Certain classic symptoms and signs, although not specific, strongly suggest rheumatic or other diseases.

Table (1): Symptoms Suggestive of Rheumatic Diseases

Symptom	Rhuematic diseases	Some possible non-rheumatic diseases causing similar symptoms
Fevers	Systemic JRA	Malignancies, infections, inflammatory bowel disease, periodic fever syndromes
Arthralgia	JRA, SLE, rheumatic fever, juvenile dermatomyositis, scleroderma	Hypothyroidism, trauma, reactive arthritis, endocarditis, other infections.
Weakness	Juvenile dermatomyositis	Muscular dystrophies, other myopathies
Malar rash	SLE	Photosensitivity dermatitis, fifth diseas
Chest pain	JRA, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis
Back pain	JRA, spondyloarthropathy	Vertebral microfracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis

(Miller, 2008)

Physical examination

The physical examination helps identify the organs involved. Because rheumatic diseases may take time to evolve, repeated examinations are important to detect new manifestations. The general appearance may suggest certain diagnoses ***(LeBovidge et al., 2005).***

Apparently isolated findings may be important clues to target organ involvement in rheumatic diseases. A pericardial friction rub with orthopnea may occur with pericarditis from lupus or systemic JRA. Persisting oral mucosal lesions are found in lupus and Behçet disease.

Other mucous membrane involvement such as, swollen tongue or lips, raises the possibility of Kawasaki disease, Stevens-johnson syndrome, and scarlet fever. Conjunctival injection could be episcleritis of lupus, conjunctival inflammation of Kawasaki disease, or uveitis ***(Lehman, 2005).***

Although persistent joint complaints suggest JRA, other rheumatic diseases, including lupus and dermatomyositis, can also present with arthritis. All children with joint symptoms should be asked about muscle weakness, which is characteristic of dermatomyositis and mixed connective tissue disease ***(Troyanov et al., 2005).***

Although the rheumatic diseases sometimes can present with non-specific symptoms, especially early in the course, each disease over time develops a characteristic set of symptoms and physical findings that can be elicited by careful history and physical examination. These data, in conjunction with carefully chosen confirmatory laboratory tests, help develop the appropriate differential diagnosis and eventually determine the correct diagnosis and treatment plan ***(Anthony and Schanberg, 2005).***

The correct diagnosis is imperative to prevent any long-term disability associated with untreated chronic inflammation ***(Haftel, 2006).***

The following are criteria of diagnosis and classification of common connective tissue diseases in pediatrics

Table (2): Diagnostic criteria of SLE

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised over malar eminencies, sparing the nasolabial folds.
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring may occur in older lesions.
3. Photosensitivity	Skin rash is a result of unusual reaction to sunlight by patient history or physician observation.
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician.
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion.
6. serositis	a. Pleuritis convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or b. Pericarditis, documented ECG or rub or evidence of pericardial effusion.
7. Renal disorder	a. Persistent proteinuria greater than 0.5 gm/day or greater than 3+ if qauantitation not performed. b. Celullar casts may be red cells, granular, hemoglobin, tubular or mixed.
8.Neurological disorders	a. Seizures in absence of offending drugs or known metabolic derangement : e.g : uremia, ketoacidosis, or electrolyte imbalance, or b. Psychosis in absence of offending drugs or known metabolic derangement : e.g : uremia, ketoacidosis, or electrolyte imbalance.
9.Hematological disorders	a. Hemolytic anemia with reticulocytosis or b. Leukopenia less than 4000/mm3 on more than two occasions or c. Thrombocytopenia less than 100.000/mm3 in absence of offending drugs or d. Lymphopenia less than 1500/mm3 on more than two occasions.
10.Immunological disorders	a. Positive LE cell preparation or b. Anti-DNA antibody to native DNA in abnormal titre, or c. False positive serological test for syphilis known to be positive for at least six months and confirmed by Treponema pallidum immobilization or florescent treponemal antibody test.
11.Antinuclear antibody	An abnormal titre of antinuclear antibody by immunefluorescence or an equivalent assay any point in time in the absence of drug.

(Tan et al., 1982)

Table (3): Criteria for the classification of Juvenile chronic arthritis (JCA) or Juvenile Idiopathic arthritis (JIA) by the International League against Rheumatism (ILAR):

- Length of illness before diagnosis: 6 weeks and classified into:
- Systemic JCA.
- Polyarticular JCA, RF positive.
- Polyarticular JCA, RF negative.
- Oligoarticular JCA which classified into:
- Persistent (1 to 4 joints).
- Extended (eventually affecting 5 or more joints)
- Psoriatic arthritis.
- Enthesis-related arthritis.
- Other arthritis.

(Petty et al., 2004)

Table (4): Criteria for diagnosis of juvenile dermato-myositis: (4 of 5 criteria are required to make definitive diagnosis)

- Rash typical of dermatomyositis
- Symmetric proximal muscle weakness
- Elevated muscle enzymes (SGOT, SGPT, LDH, CPK, and aldolase
- EMG abnormalities typical of dermatomyositis (fasciculations, needle insertion irritability and high frequency discharge)
- Positive muscle biopsy specimen with chronic inflammation

(Haftel, 2006)

Laboratory studies

Evidence of an underlying systemic inflammation may be indicated by elevated acute phase reactants, especially the erythrocyte sedimentation rate (ESR), but also the white blood cell count (WBC), platelet count, and C- reactive protein (CRP). The complete blood count may show evidence of a normochromic, normocytic anemia of chronic disease. All of these laboratory findings are nonspecific for any particular rheumatologic diagnosis. Certain laboratory tests may help confirm a diagnosis such as, autoantibody production in SLE or enzyme elevation in juvenile dermatomyositis ***(Pachman et al., 2006)***.

The ANA test (antinuclear antibodies) is a screening test for specific antibodies against nuclear constituents. A positive titer is a non-specific reflection of increased lymphocyte activity. Positive ANA tests are found in children with rheumatic diseases and other diseases such as, idiopathic thrombocytopenic purpura, Crohn disease, chronic autoimmune hepatitis, Graves disease and, rarely, leukemia or lymphoma ***(D'Cruz, 2006).***

The antinuclear antibodies to specific nuclear antigens may help in differential diagnosis of certain connective tissue diseases as shown in **Table (5).**

Other immunological laboratory tests, although not diagnostic of rheumatic disease, are useful in characterizing

the extent of immune activation and monitoring response to therapy. Levels of total hemolytic complement (CH50), C3 and C4 are characteristically decreased in active lupus and vasculitis syndromes ***(Burt et al., 2006).***

Table (5): The antinuclear antibodies to specific nuclear antigens

Antinuclear antibodies	**Associated manifestations**
Single-stranded DNA	Non-specific, indicates inflammation
Double-stranded DNA	SLE, renal disease
DNA-histone	Drug-induced SLE
Sm (Smith)	SLE, renal or CNS disease
RNP (ribonucleoprotein)	SLE, Sjögren syndrome, scleroderma, polymyositis and mixed connective tissue diseases
Ro (Robert: SSA)	SLE, neonatal lupus-congenital heart block, Sjögren syndrome
La (Lane: SSB)	SLE, Sjögren syndrome
Jo-1	Polymyositis, dermatomyositis
Scl-70	Scleroderma
Centromere	CREST syndrome variant of scleroderma
PM-Scl	Scleroderma, undifferentiated connective tissue diseases

(Haftel, 2006)

In general, 15 to 20% of children with JRA are seropositive for rheumatoid factors (RFs) ***(Cassidy and Petty, 2000),*** although, RFs are neither specific nor diagnostic of RA. They also occur in other rheumatic

diseases (SLE, Scleroderma), chronic infections (such as, bacterial endocarditis, parasitic infestations), leukaemia and some viral infections. In addition, they can be detected following immunization ***(Pachman et al., 2006).***

Immune activation may be reflected by elevated levels of immune complexes, serum immunoglobulins, neopterin (a macrophage product), and von Willebrand factor antigen (a molecule found on the surface of vascular endothelium) ***(Miller, 2008).***

Lactate dehydrogenase levels may be elevated in rheumatic diseases as a result of cell turnover, and marked elevations raise the possibility of malignancy ***(Tucker and Cabral, 2005).***

Diagnostic imaging

Radiological studies should focus on areas of concern identified by history or physical examination. Radiography of joints in patients with arthritis on examination may be beneficial, but radiographic abnormalities may lag far behind the clinical examination. More sensitive tests such as, bone scan, CT scan, and MRI, may be useful when trying to differentiate between frank synovitis from traumatic soft tissue injury. MRI also can be useful to identify evidence of CNS involvement with SLE or for evidence of myositis with juvenile dermatomyositis ***(Bader-Meunier et al., 2005).***

Treatment of rheumatic diseases

Treatment of children with rheumatic diseases is complex and challenging. The efforts of a team of health care professionals need to be melded into a coordinated system of management that is individualized to meet the needs of each patient and is sensitive to the capabilities and psychological resources of the family.

Disease manifestations for each child during the course of the disease can vary in severity over time, treatment must be adjusted accordingly. The therapeutic program must provide appropriate therapy for current symptomatic problems, such as, arthritis, as well as include appropriate screening methods for often clinically silent complications such as, uveitis in children with JRA and early nephritis in patients with SLE ***(Avon et al., 2006).***

The goals for treatment are to maximize the daily functional activities of affected children, relieve discomfort, prevent or reduce organ damage, and avoid or minimize drug toxicity ***(LeBovidge et al., 2005).***

Medications used for treatment of childhood rheumatic diseases (**Table 6**) have various mechanisms of action, but all share the ability to suppress inflammation. Disease- modifying anti-rheumatic drugs addresses the autoimmune process and includes methotrexate and

biologic products against Tumor necrosis factor-α and other mediators of inflammation ***(Lovell et al., 2008).***

Future treatments

Rheumatologist commonly combine several drugs in the treatment of rheumatic diseases to achieve better disease control, often to permit the use of a lower dose of steroids. In addition to inhibitors of TNF, a wide variety of other biological agents are being studied in adults and many more are in development to modulate individual cell populations or molecular species involved in inflammatory processes. Monoclonal antibodies that can suppress specific T-cell subpopulations, bind particular cytokines or cytokine receptors (IL-1 and IL-6), bind antibody-producing B cells, or inhibit anti-double-stranded DNA autoantibodies are being widely tested in adults with rheumatic diseases primarily lupus and rheumatoid arthritis. The potential for these therapies in children with rheumatic diseases is great but largely untested at this time ***(Hashkes and Laxer, 2005).***

Table (6): Cornerstones of Treatment of Children with Rheumatic Diseases

Accurate diagnosis and education of the family	• Pediatric rheumatologist • Pediatrician • Nurse • Social worker
Medications	• Non-steroidal anti-inflammatory drugs (NSAIDs) • Methotrexate • Tumor necrosis factor-α blockers • Modulate T-cell activation • Anti-CD20 (B-cell) antibody • Interleukin-1- receptor antagonist • Hydroxychloroquine • Sulfasalazine • Intravenous immunoglobulin (IVIG) • Cyclophosphamide • Cyclosporine • Glucocorticoids (oral, intravenous, pulse, ophthalmic, intra-articular) • Chaperonin-10 (inhibits toll-like receptors)
Stem cell transplantation	Experimental approach to treatment-resistant lupus or JRA
Physical medicine and rehabilitation	• Physical therapy • Occupational therapy • Splints and reconstructive surgery
Physical and psychological growth and development	• Nutrition • School integration • Peer group relationships • Individual and/or family counseling
Coordination of care	• Involvement of patient and family as critical and active team members • Communication between the pediatric rheumatologist and pediatrician • Involvement of school (school nurse) and community resources (social worker)

(Lovell et al., 2008)