Overview Of Connective Tissue Diseases And Juvenile Idiopathic Arthritis In Children

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ABSTRACT

Paediatric connective tissue diseases (PCTD) and juvenile idiopathic arthritis (JIA) have been investigated and reported extensively among Western children compared with low frequency of reports among African children. This may be due to reduced awareness among African general practitioners; paucity of Paediatric rheumatologists in most Africa countries; little or no laboratory back up; and the belief that CTD and arthritis are not diseases of children. This article aims at discussing the general approach to CTDs and chronic arthritis in children; as well as increase awareness among doctors in Africa.

INTRODUCTION

Connective tissue diseases (CTDs) and juvenile idiopathic arthritis (JIA) are chronic inflammatory multisystemic rheumatic diseases associated with exaggerated immune response. The consequence of heightened immune activation is damage to articular, connective tissues and extra-articular organ structures. CTDs have predominant autoimmune basis with serological evidence of auto-antibodies against various tissues antigens and it includes Juvenile Systemic lupus erythematosus(JSLE), Juvenile Dermatomyositis(JDM), Neonatal Lupus Syndrome(NLS), Paediatric Sjogren's syndrome(PSS) and Juvenile systemic sclerosis(JSSC); while JIA is predominantly an auto-inflammatory disease with little or no identifiable antibodies, starting before the sixteenth birthday, and characterized by arthritis of at least one joint for 6 weeks or more.[1] These conditions have been studied and reported

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extensively among Western children with clinical course, manifestations, prognosis and severity, quite distinct from adult diseases. While some conditions such as systemic JIA, JSLE, and JDM may present with life threatening organ manifestations, others are associated with long term disability, chronic anterior uveitis, amyloidosis and adverse effects of chronic steroid and immunosuppressive administrations.[2]

Access to paediatric rheumatology service in Sub-Sahara Africa is limited, with major challenges such as lack of a multi-disciplinary team, with special training in rheumatology; as well as lack of diagnostic and therapeutic resources .Other challenges include notions that arthritis does not occur in children and diagnostic difficulties posed by common paediatric conditions in Africa such as haemoglobinopathy; acute leukaemia; acute rheumatic fever, and haemophilia; mimick CTDS and JIA. This has hampered epidemiological report from Africa, with little or no national prevalence studies, thus many cases of chronic arthritis and CTD in children going undiagnosed and thus untreated.

The prevalence of JIA in a Nigerian hospital based study was 1.3% while a prevalence rate of 33% was documented among South African children with JIA children.[3] The delay in recognition and diagnosis is considered a major stumbling block in achieving optimal outcome in paediatric rheumatic care with lasting effect on health, psychological and functional development; as well as socio-economic well-being throughout life.

The aim of this review was to highlight the epidemiology of paediatric rheumatological conditions; with emphasis on African children, aetio-pathogenesis, classification, clinical and laboratory features, as well as general principle of management of CTDs and JIA. We hope this review will help create awareness and improve our evaluation and management of children with rheumatic conditions.

EPIDEMIOLOGY

It is difficult to accurately establish the prevalence and incidence of CTDs and JIA in defined populations, as most of the studies were from rheumatology clinic settings.[4] Rheumatic conditions can be found in all paediatric age groups, with female preponderance. In general, the spectrum of CTDs and JIA has been poorly reported in Africa; however, clinical patterns of

JIA have been reported in few hospital based studies from Nigeria and South Africa.[5] Oligo-articular JIA was the commonest JIA documented in most non- Nigerian studies; while poly-articular JIA was the predominant subtype documented in Nigerian studies. In the United States of America, JIA constituted 33.1 % of all paediatric rheumatic cases (PRC) while a prevalence of 33.3% was documented in Cape-Town, South Africa. The prevalence of JIA in UK was 60.1% while a prevalence of 1.3% was recorded in a private clinic in Lagos; consisting of a mixed adult and paediatric rheumatic population. Systemic connective tissue diseases were found in 10.4% of PRC cases studied in South Africa while childhood Vasculitis constituted 4.8% of all the cases. Case reports and series of JDM, JSLE, NLS and JIA co-existing with sickle cell disease have been reported among Nigerian children.

AETIOPATHOGENESIS

As with adult rheumatic conditions, the causes of CTDs and JIA are largely unknown; though some genetic and environmental factors have been smoking, female sex hormone, drugs, and infectious agents are possible environmental factors. Association and linkage to HLA loci and non-HLA genetic loci have been confirmed for certain childhood rheumatic diseases. The combinations of environmental and genetic factors determine the development and expression of an autoimmune disorder. Systemic CTDs such as JSLE, JDM, and JSSC develop from complex interactions between these environmental and genetic factors. These results in the loss of immunological tolerance; with resultant induction, activation, and proliferation of auto reactive T and B cells; coupled with the production of auto-antibodies and immune complex deposition in connective tissues and vital organs. Auto-inflammatory conditions such as JIA have been linked with exaggerated innate immune responses; as there are no traceable auto-antibodies in the sera of these patients. However, strong links with MHC loci; and the presence of inflammatory T cells within the inflamed synovium, support a role for adaptive immunity in the pathogenesis of JIA.

CLASSIFICATION AND NOMENCLATURES

International league of association of rheumatology (ILAR) has classified JIA into seven types. This includes **systemic JIA**; **oligo-arthritis JIA,** with 2 subtypes **(persistent and extended)**; **poly-arthritis JIA, rheumatoid factor negative; polyarthritis JIA, rheumatoid factor positive; psoriatic arthritis**; **enthesitis-related arthritis**; and **undifferentiated arthritis**. CTDs in children comprises **anti-phospholipid syndrome (APS), mixed connective tissue diseases (MCTD), localised scleroderma, JSLE, JDM, JSSC, JSS and Raynaud's phenomenon.** Arthritis can be **monoarthritis-** if only one joint is affected; **oligo (pauci) arthritis-** if two to four joints are involved; and **polyarthritis-** if five or more joints are affected. Furthermore, arthritis can be **additive -** if the affected joints are added progressively; or **migratory-** if the arthritis flits from one joint to another. Arthritis can also be **acute**- if onset is in hours or days, but usually less than six weeks; or **chronic**- if onset is over weeks or months, but usually more than six weeks. It can also be **persistent or recurrent, symmetrical or asymmetrical arthritis**. Inflammatory back pain is a form of back pain that gets worse with rest and is relieved with activity.

CLINICAL PRESENTATIONS

Typical rheumatic symptoms such as joint pain and joint stiffness may be difficult to ascertain in children. However, children with JIA usually present with joint swelling, limping, deformity, restricted play and reduced function .Children with non- systemic types of JIA present with predominant arthritis symptoms, with little or no systemic features; while children with systemic JIA and CTDs present with predominant systemic features with little or no arthritis. Constitutional symptoms of fever, weight loss and severe fatigue can be found in patients with CTDs, systemic JIA, and systemic vasculitis .Daily quartidian fever or evening fever may be suggestive of systemic JIA. Systemic JIA and CTDs may manifest with prominent features of organ dysfunction such as serositis, interstitial lung disease, heart failure, glomerulonephritis, thrombosis and central nervous system dysfunction .Identification of specific skin features such as skin sclerosis, Raynaud' signs,

telangiectasia (in systemic sclerosis ,localised scleroderma, MCTD), photosensitive rash, malar rash, discoid rash (SLE), Gottron's papule or sign ,heliotrope rash(dermatomyositis), palpable purpura, digital ulcers, nodules (secondary vasculitis), genital ulcers, oral ulcers (SLE), Sicca's symptoms (Sjogren's syndrome), salmon pink evanescent erythematosus rash (Still's disease or systemic JIA), and diffuse swelling of the hands or feet (MCTD, systemic sclerosis) can facilitate early diagnosis.

INVESTIGATIONS

The most common use of haematology and acute phase reactant tests is for monitoring side effects of the various immunosuppressive medications used for the treatment of rheumatic conditions. Some haematological abnormalities can however help in the differential diagnoses and monitoring disease activity of certain CTDs and JIA. Leucocytosis and thrombocytosis may suggest JIA, especially systemic JIA. It can also be seen in other JIA mimics such as primary vasculitis, periodic fever syndrome, and infectious arthritis. Absence of blast cells in marrow aspirate with leucocytosis may exclude acute leukaemia. Lymphocytosis may be a pointer to viral arthropathy. Thrombocytopenia, lymphopenia, and neutropenia may indicate SLE, macrophage activating syndrome or drug induced bone marrow suppression. Anaemia of chronic disease and iron deficiency anaemia may indicate chronic inflammatory rheumatic diseases or result from gastrointestinal bleeding from steroid or NSAID therapy respectively. Auto-immune haemolytic anaemia may indicate SLE and other CTDs.Acute phase reactants such as erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), serum ferritin and C3 complements are used to monitor disease activity and response to therapy. Elevated CRP, ESR, serum ferritin and C3 complements may be found in systemic JIA with high disease activity. However, it may also indicate poor response to therapy. CRP or ESR levels may be normal in about one-third of JIA cases. Acute phase reactants can also be elevated in cases of infection and vasculitis. Serum concentrations of MRP-8/MRP-14 have been reported to be useful in differentiating systemic JIA from infections and other possible causes of systemic inflammation .SLE and other CTDs with immune complex deposition may be associated with low C3 complement level.

Serology tests such as rheumatoid factors (RF) and antinuclear antibody (ANA) are not required for diagnosis of JIA; however, they can be used to classify JIA or determine the risk of uveitis. ANA and extractable nuclear antibody (anit-dsDNA, anti-sm, anti-u1RNP, anti-SCL-70, anti-JO1, anti-RO, and anti-LA) may be detected in high titre in CTDs. Synovial fluid culture may be useful in suspected cases of secondary septic arthritis. Plain radiographs of affected joints are not useful for diagnosis of CTDs and JIA; but it can be used to identify complications such as erosions, osteopenia, pathologic fractures, avascular necrosis, ankylosis, osteomyelitis, and subluxation especially in long standing disease. Cardiac involvement in JIA and CTDs can be detected using echocardiography while abdominal ultrasound can be used to exclude neuroblastoma .Elevated muscle enzymes such as creatine kinase and aldolase may indicate myositis. Calcium and vitamin D level, liver biochemistry, renal function test and urinalysis are indicated to monitor adverse drug effects or disease complications. Biopsy of affected organs is useful in suspected cases of lupus nephritis, secondary vasculitis, and JDM.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSES

Diagnosis of CTDs and JIA is based on fulfilment of validated classification criteria for specific rheumatic conditions and exclusion of other common mimics. American College of Rheumatology (ACR), European Union League against Rheumatism (EULAR) and International League of association of Rheumatology (ILAR) have proposed criteria for CTDs and JIA while some are diagnosed using adult criteria and other well established criteria .Common paediatric conditions such as haemoglobinopathy, malignancy, haemophilia, infection, acute rheumatic fever and ,infective endocarditis are the main differential diagnoses. However, rare diseases such as childhood vasculitis, auto-inflammatory syndrome, inflammatory bowel disease and sarcoidosis must be excluded. Classification criteria for JIA, JDM and SLE are highlighted in the table below.

Table 1: Classification criteria for JIA, JDM and SLE

ILAR criteria/ classification	ACR 1997 Classification criteria for SLE[25]	Classification criteria for Dermatomyositis[24]
Primary definition of JIA: Definite arthritis of unknown aetiology that begins before the 16th birthday and persists for at least 6 weeks. Categories of JIA 1.Systemic arthritis 2. Oligoarthritis a. Persistent oligoarthritis b. Extended oligoarthritis 3. Polyarthritis (rheumatoid factor negative) 4. Polyarthritis (rheumatoid factor positive)	1.Malar rash 2. Discoid rash 3. Photosensitive rash 4.Oral ulcers 5. Arthritis 6. Serositis 7.Renal disorder: 3 +proteinuria or greater or equal to 0.5g/day proteinuria or cellular cast 8.Neurological Disorder: seizure, psychosis or headache 9.Hematological disorder: haemolytic anemia with reticulocytosis, thrombocytopenia or leucopenia or lymphopenia	1.Symmetrical weakness of the proximal musculature 2. Characteristic cutaneous changes consisting of heliotrope discoloration of the eyelids, which may be accompanied by periorbital edema and erythematous papules over the extensor surfaces of joints, including the dorsal aspects of the metacarpophalangeal and proximal interphalangeal joints, elbows, knees, or ankles (i.e., Gottron papules) 3. Elevation of the serum level of one or more of the following skeletal muscle enzymes: creatine kinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase

5. Psoriatic arthritis 6. Enthesitis related arthritis 7. Undifferentiated arthritis	10.Immunological Disorder:positive antidsDNA in high titre or positive anti-sm or positive anti-phospholipid antibodies 11.Antinuclear Antibody:abnormal titre of antinuclear antibody Definite SLE: At least Four out of eleven Criteria NB: Criteria should be applied in the absence of other causes.	4. Electromyographic demonstration of the characteristics of myopathy and denervation, including the triad of polyphasic, short, small motor-unit potentials; fibrillations, positive sharp waves, increased insertional irritability; and bizarre, high-frequency repetitive discharges 5. Muscle biopsy documenting histological evidence of necrosis; fiber size variation, particularly perifascicular atrophy; degeneration and regeneration; and a mononuclear inflammatory infiltrate, most often in a perivascular distribution. Definite Dermatomyositis:Skin changes including any other three features in the criteria. NB: Criteria should be applied in the absence of other causes.

COMPLICATIONS

Chronic anterior uveitis is the major cause of progressive visual loss and blindness in patients with JIA; especially the ANA positive oligo-articular type. Macrophage activating syndrome is a life threatening complication of systemic JIA and is a major cause of mortality .Dental decay, chronic anaemia, osteoporosis, growth disturbance, deformities, sepsis, premature atherosclerosis, Reye's syndrome, secondary vasculitis and APS, amyloidosis, poor therapeutic adherence, inability to complete the tasks of adolescence and disenfranchisement with the medical system are other documented complications of CTDs and JIA.

MANAGEMENT OF CHILDHOOD RHEUMATIC CONDITIONS

In general, the aims of management are:[1] to induce remission or lower disease activity [2] to relieve symptoms or discomfort[3] to preserve function and prevent deformity[4] to maintain remission and[5] to prevent and treat complications. Multi-disciplinary approach should be the goal.

The paediatric health team should be led by the paediatric rheumatologist working in concert with other members of an extended specialist health team such as Ophthalmologists, Nephrologists, Endocrinologists and Orthophedi surgeons. Assessment tools for disease activity, function, damage and quality of life have been developed for certain CTDs and JIA; however, majority yet to be validated. Baseline assessment of disease activity and damage is important before the institution of drug therapy.

Most of the drug treatment guidelines in CTDs and JIA were extrapolated from adult protocols as there is paucity of randomised controlled trials in paediatric age group.

NSAID, corticosteroids, synthetic disease modifying anti-rheumatic drugs (DMARD), biologic DMARDs and immunomodulators are group of drugs that have been employed in the treatment of CTDs and JIA. Complete blood count, liver transaminases, serum creatinine, and ophthalmological examination should be done at interval to monitor drug toxicity.

NSAIDs provide symptomatic anti-inflammatory, analgesic and anti-pyretic effect; however, they do not have disease modifying

effects; thus they are recommended for most patients with JIA. Indomethacin is used in the treatment of fever or pericarditis in systemic JIA .Serious toxicity associated with NSAIDs is rare in children.

Corticosteroid drugs are the most potent anti-inflammatory agents used in the treatment of rheumatic diseases. The overall aim is to limit the dose and duration of steroid therapy to the lowest possible levels, while achieving disease control. Administration of a single dose in the morning and use of alternate-day regimens, which have been shown to minimize the suppression of linear growth in children, should be adopted whenever possible. In JIA, the use of systemic glucocorticoids is mainly limited to treating the extra-articular features of systemic JIA. Low-dose, short-term systemic glucocorticoids may also be indicated in severe forms of polyarticular JIA with significant functional impairment; as well as for chronic uveitis unresponsive to local therapy. High-dose systemic glucocorticoids are used in children with JSLE and JDM. Intravenous glucocorticoids "pulse" therapy is sometimes used to treat more severe, acute, systemic connective tissue diseases such as SLE, JDM, macrophage activation syndrome and refractory systemic features of systemic JIA. Intra-articular steroid injection is indicated for patients with active synovitis or effusion in 1-2 joints.

Synthetic DMARDs have disease modifying effect and are used to treat JIA and certain CTDs; exerting their beneficial effects weeks to months after initiation of therapy. These compounds include methotrexate (MTX), antimalarials, sulfasalazine, leflunomide, gold compounds, azathioprine, cyclosporine, cyclophosphamide (CXC), mycophenolate mofetil (MMF) and penicillamine. MTX is the most commonly used DMARD for JIA. Several DMARDs are also used to treat other rheumatic diseases (e.g., MTX in JDM, systemic sclerosis and uveitis; hydroxychloroquine in the management of SLE, Azathioprine in JIA and SLE, MMF in SLE, CXC in proliferative lupus nephritis and life threatening vasculitis).

Biologic DMARDs are monoclonal antibodies, fusion receptors and peptides that target specific cells or molecules in the inflammatory cascades. Some of these agents have been approved for refractory JIA. Etanercept, adalimumab, infliximab, abatacept, tocilizumab, and rituximab are indicated for JIA unresponsive to

standard treatment.Intravenous immunoglobulin (IVIG) is prepared from pooled human plasma. It has been used in JDM, SLE, and systemic JIA. Supportive measures include administration of Growth Hormone, Calcium and Vitamin D supplementation in all patients with JIA and CTDs on steroids. Use of sun screen ,anti-hypertensive agents and anti-proteinuric drugs in patient with lupus nephritis, use of statins, anti-platelets and anticoagulants when indicated .Non pharmacology measures such as patient and family education, transition to adolescent-plan, rehabilitation therapy, and orthopaedic procedures are integral parts of the management of these children.

PROGNOSIS

One half of children with chronic arthritis have the active disease up to 10 years after onset. 30% of these children continue to have active arthritis into their adult years. Cumulative organ damage occurs in 50% to 60% of JSLE, along with a poorer health-related quality of life and lower socioeconomic achievements than their healthy peers. Though the ten-year survival rate markedly improved in recent decades, mortality in JSLE remains higher than in adults.

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