INTRODUCTION

Juvenile idiopathic arthritis (JIA), previously called juvenile chronic arthritis or juvenile rheumatoid arthritis, not a disease but an exclusive diagnosis that includes all forms of chronic and unknown origin with onset before 16 years of age **(Adams et al., 2005 and Hahn et al., 2010).**

JIA recompresses a number of articular inflammatory diseases with distinct methods of presentation, clinical signs, and symptoms, and in some cases, genetic background, they all share the occurrence of chronic inflammation within synovial joints in children below 16 years of age and for at least 6 weeks **(Dannecker et al., 2009)**

Considering the inflammatory reactions seen in JIA patients, several genes involved in immune reaction become potential candidates to genetic studies. Genes and proteins related to metabolization/detoxification of xenobiotic are commonly used as potential markers of susceptibility for the development of several diseases in which the etiology is related to exposure to environmental hazards **(Starks el al., 2010).**

Genes coding for enzymes responsible for activation (phase I reactions) or deactivation (phase II reactions) of xenobiotic are potential targets. The glutathione S- transferases

(GSTs) are a supergene family involved in phase II of biotransformation that protects cells against endogenous and exogenous metabolites **(Morinobu et al., 2006 and Prahalad et al., 2008).**

There is evidence that gene polymorphism is associated with differences in detoxification efficiency which has been involved in the susceptibility, severity and clinical outcome of JIA **(Xavier et al., 2008 and Hinks et al., 2010)**

AIM OF THE STUDY

The present study is carried out to explore the association between glutathione S transferase genes and susceptibility to juvenile idiopathic arteritis.

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic disease of children and a major cause of disability. It is characterized by an idiopathic synovitis of peripheral joints associated with soft tissue swelling and effusion **(Deslandre, 2016).**

The older terms juvenile rheumatoid arthritis (JRA, used commonly in USA) and juvenile chronic arthritis (JCA, preferred in Europe), have been replaced by the term juvenile idiopathic arthritis (JIA). It incorporates all of what was called JRA in the past, and also includes all other forms of "idiopathic" arthritis in childhood (**Oberle et al., 2014).**

The disease primarily affect the joint but can also cause heavy damage to organs and systems such as the heart, blood vessels, skin, eyes, and peripheral nerves **(Meholjic-Fetahovic, 2005).** Moreover, anti rheumatic drugs have limited efficacy, many side effects and do not improve the long-term prognosis of the disease **(Loetscher and Moser, 2002).**

Age of onset:

JIA begins before the age of 16 years. Even though onset before 6 months of age is unusual, the age of onset is characteristically young (1-3 years) but with a substantial

number of cases beginning throughout childhood. Systemic onset is an exception with no increased frequency at any particular age (**Oberle et al., 2014).**

Epidemiology

JIA is one of many chronic inflammatory diseases that predominate in females. The ratio of female: male patients ranges from 2: 1 - 4: 1 except, for systemic onset type in which the sex ratio is equal. About 30 - 50 % concordance rate has been reported in monozygotic twins when one twin is affected compared with 1% for the general population. The risk for a fraternal twin of a patient with JIA is also high (2-3 %), but this is not more than the rate for other first-degree relatives **(Cassidy, 2001).**

The average annual incidence of JIA in public allergy and immunology unit of Ain Shams University was reported to be 10.3/100, 000 children per year (**Hosney et al., 2006).**

One of the Egyptian studies showed that there were some differences and some similarities in the clinical profile of Egyptian patients with (JIA) when compared to other populations. The mean age of disease onset was 6.257 ± 3.41 years. Disease prevalence was almost equal in patients from both urban and rural areas in contrary to other studies. The pauciarthritis was the most frequently observed type followed by polyarticular type **(Salah et al., 2009).**

Etiology & pathogenesis:

JIA is a complex genetic trait disease involving the effects of multiple genes related to immunity and inflammation. Arthritis may be triggered in a genetically predisposed individual by psychological stress, abnormal hormone levels, trauma to a joint, bacterial or viral infection **(Weiss and Ilowite, 2005).**

1-Infection:

Table (1): The possible infectious agents that may be incriminated in the pathogenesis of JIA.

Infectious agent	Potential pathogenic mechanisms
Mycoplasma	Direct synovial infection; superantigens
Parvovirus B19	Direct synovial infection
Retrovirus	Direct synovial infection
Enteric bacteria	Molecular mimicry
Mycobacteria	Molecular mimicry
Epstein-Barr virus	Molecular mimicry
Bacterial cell walls	Macrophage activation.

(Cassidy, 2001)

Although an infectious etiology has been speculated, no organism has been proven responsible **(Smith and Smolen, 2006).**

Bacterial heat shock proteins are targets to specific humoral and cellular responses in patients with JIA. The intensity of these responses correlates significantly with the degree of activity of the disease.

2- Trauma:

- **Physical trauma:**

JIA has been reported by parents to follow minor physical trauma to an extremity. Such trauma may serve as a localizing factor or it may call attention to an already inflamed joint **(Miller and Cassidy, 2004).** The fact that certain joints (e.g. knee in pauciarticular JIA) are most frequently affected could suggest that the physical trauma is associated with weight bearing joints which may play a factor in initiating chronic inflammation, however the precise role of trauma remains unknown **(Cassidy and Petty, 2000)**.

- **Psychological trauma:**

It is well documented that psychological stress is particularly common in families of children with JIA **(Barlow et al., 2001 and O'Dell, 2007).**

3-Immunologic factors:

Immunologic abnormalities in JIA include production of autoantibodies, abnormalities in cytokine network and immune

responses to infectious agents. Complement activation and consumption probably play a role in the inflammatory reaction (**Grom and Hirsch, 2000).**

A- T lymphocytes:

T-cell activation is the first major step in the pathogenesis of the disease and results in release of interleukins, interferon-γ, granulocyte colony-stimulating factor (GM-CSF) and other proinflammatory cytokines**.** $CD4^{+,}$ $CD25^{+}$, T regulatory cells was suggested to play a role in determining the disease prognosis. **(De Kleer et al., 2004)**.

JIA was considered as an autoimmune disease based on identification of rheumatoid factors (RF) in the sera of patients. It is characterized by production of RF in the synovium and the formation of RF immune complexes with the recruitment of a variety of cells (T cell**,** B cell and macrophages) where they become activated and contributed to joint inflammation and damage **(Newton et al., 2004)**. **Macaubas and colleages (2009)** demonstrated a relationship between rheumatoid arthritis (RA) and a specific human leukocyte antigen (HLA-DR) genes of the major histocompatibility complex (MHC)**.**

- B-lymphocytes:

B Lymphocytes numbers are normal to be increased in children with JIA depending on onset type**.** Immunoglobulin

levels tend to be high, reflecting the nonspecific inflammatory response **(Cassidy and Petty, 2000)**.

4- Genetic factors:

Genetic basis of JIA is complex in nature; there may be certain genetic factors that predispose to onset at a young age and other genes that determine precisely what form or subgroup of JIA manifests **(Miller and Cassidy, 2004).**

Each of the JIA subtypes has a distinct human leukocyte antigen (HLA) association indicating some genetic predisposition to disease. Pauciarticular with HLA-DRW8, HLA-DR5 and HLA-DRW6, and (RF) positive disease with HLA-DR4. Significant associations were found with HLA-A2, HLA-DR5, and HLA-DR8. A significant excess of HLA-DR5-DR8 heterozygotes was also found. Interestingly, HLA-DR7 and HLA-DR4 were protective, seen less frequently in patients compared with the controls **(Smerdel et al., 2002).**

Ezzat et al., (2005), reported the association of DRB1 04, and 14 null alleles with JIA susceptibility, and DRB108 null allele with protection.

5- Oxygen radicals and tissue damage:

Increased oxidative stress in children with JIA is evidenced by a high production of nitric oxide **(Lotito et al., 2004)**. A cascade of events may lead to tissue damage, including B-cell

activation, complement consumption, and release of interleukin-6 (IL-6), IL-13, tumor necrosis factor alpha (TNF-α) and other proinflammatory cytokines. Iron can be found in the rheumatoid synovial membrane, which may promote damage probably through the production of oxygen free radicals and the release of lysosomal enzymes **(El-Gamal et al., 1990 and Miller and Cassidy, 2004)**.

Cytokines abnormalities:

JIA is associated with significant and constant changes in serum levels of cytokines and soluble receptor. The production of various pro inflammatory cytokines results in the release of chemical mediators, which cause tissue damage and play a central role in joint inflammation and systemic affection in JIA**.**

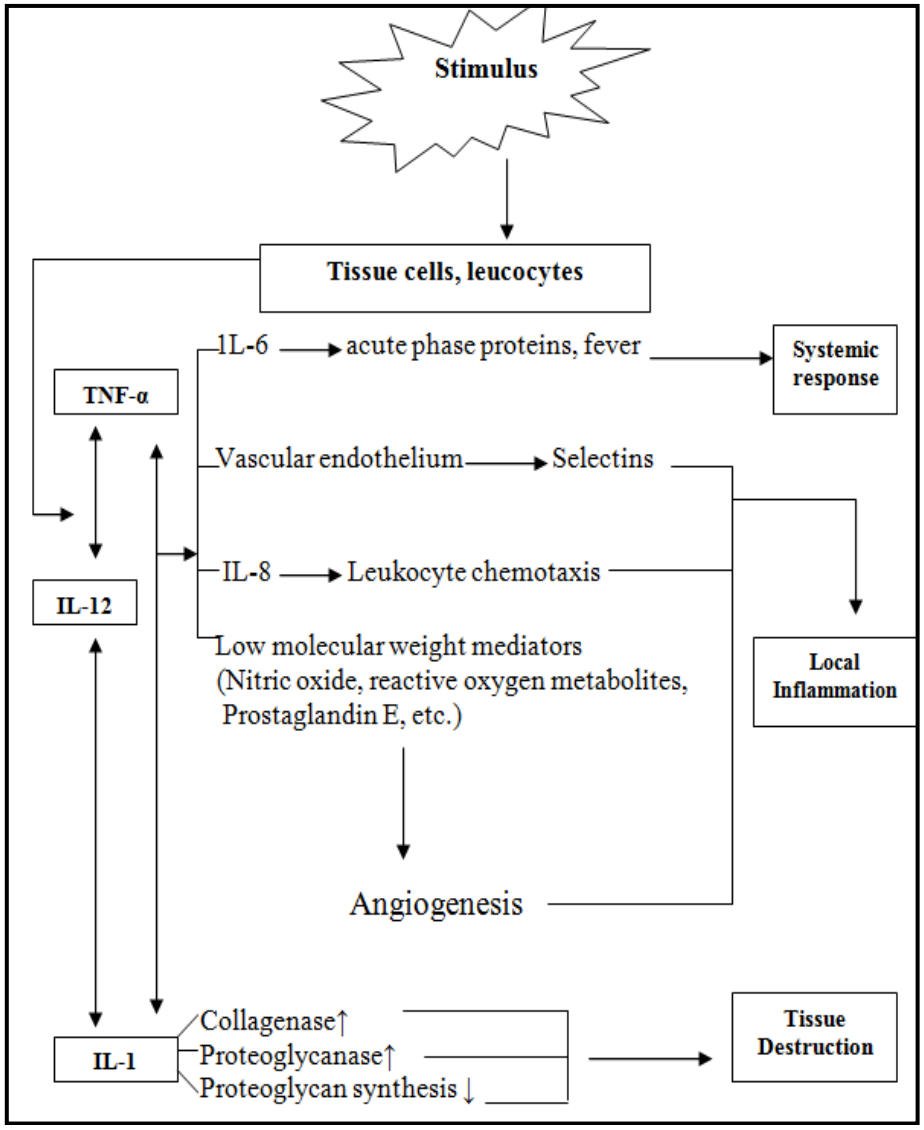

Fig. (1): A simplified scheme of inflammatory mediators showing the "hierarchy" of cytokine **(Woo, 2002).**

6-Angiogenesis and tissue destruction:

The arthritic synovium is a very hypoxic environment, which is a potent signal for the generation of new blood vessels (angiogenesis). The expansion of the synovial lining of joints in RA and the subsequent invasion by the pannus of underlying cartilage and bone necessitate an increase in the vascular supply, to cope with the increased requirement for oxygen and nutrients. Angiogenesis is recognized as a key event in the formation and maintenance of the pannus in RA and is generally accepted to be central in maintaining and promoting RA **(Walsh and Pearson, 2001).**

Table (2): Angiogenic Inducers and Inhibitors.

Proangiogenic cytokines and growth factors	**Angiogenic Inhibitors**
-Hepatocyte growth factor (HGF) -Platelet-derived growth factor (PDGF) -Platelet-derived endothelial cell growth factor **(**PD-ECGF**)** -Angiogenin -Interleukin-2 (IL-2) -Epidermal growth factor (EGF) -Insulin growth factor-1 (IGF-1) -Granulocyte colony-stimulating factor (G-CSF) -Granulocyte-macrophage colony-stimulating factor (GM-CSF) -Acidic/basic fibroblast growth factor (FGF) -Vascular endothelial growth factor (VEGF) -Transforming growth factors α and β (TGF) -Tumor necrosis factor-α (TNF-α) -Angiopoietin I	-Platelet factor-4 (PF-4) -Interferon-inducible protein 10 (IP-10) -Monokine induced by interferon-γ -Thrombospondin -Fibronectin -Prolactin -Angiostatin plasminogen fragments -Pro-peptides of type I collagen -Platelet factor-4 fragment -Epidermal growth factor fragment -Endostatin fragment of type VIII collagen

(Walsh and Pearson, 2001)

Diagnosis of JIA:

Clinical diagnosis:

Criteria for the classification of JIA:

JIA is was diagnosed using the American College of Rheumatology (ACR) 1987 revised criteria that are primarily based on clinical parameters **(Poulsom and Charles, 2007)**, recently another classification was presented by the American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis.

Table (3): Criteria for the classification of JIA (1987)

The criteria for diagnosis of JIA are:
• Age of onset less than 16 years. • Arthritis in ≥ 1 joints defined as swelling or effusion or as the presence of ≥ 2 of the following signs: Limitation of range of motion, tenderness or pain on motion and increased heat. • Duration of illness not less than 6 weeks. • Type of onset of disease during the first 6 months classified as: • Polyarticular: 5 joints or more. • Pauciarticular: 4 joints or less. • Systemic disease: with arthritis and intermittent fever.

(Miller and Cassidy, 2004)

Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of >6/10 is needed for classification of a patient as having definite RA)

Table (4) The 2010 American College of Rheumatology/ European League against Rheumatism classification criteria for rheumatoid arthritis Score.

A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

ACPA =Anticitrullinated Protein Antigens.

Clinical diagnosis:

-Morning stiffness:

Morning stiffness is a common manifestation of inflammatory joint disease (**Labyak et al 2003).**

-Pain:

Pain is a predictor of well being in children with JIA **(Sallfors et al, 2004)**. The child may not complain of pain at rest, but active or passive motion of a joint elicits pain, particularly at the extremes of the range of motion **(Palermo et al., 2004)**.

- Joint inflammation:

Any joint can be affected by JIA. The affected joint exhibits the cardinal signs of inflammation, swelling, erythema, hotness, pain and loss of function **(Shepherd et al., 2016).**

- Tenosynovitis:

Tenosynovitis is a manifestation of active disease. Inflammation of the tendon sheaths develops principally over the dorsa of the wrists and around the ankles. **(Shepherd et al., 2016).**