BIOCHEMICAL AND GENTIC STUDY OF EGYPTIAN PATIENTS WITH MUCOPOLYSACCHARIDOSIS

Thesis
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Introduction

The mucopolysaccharidosis (MPS) are a group of heritable disorders each of which is produced by a deficiency of an enzyme required for the lysosomal degradation of sulfated glycosaminoglycans ***(Neufeld and Meenzer, ٢٠٠١).***

Mucopolysaccharides (or glycosaminoglycans) are large macromolecules composed of repeating frequently sulfated, disaccharide units attached to a protein core. A series of lysosomal acid hydrolases degrades the glycosaminoglycans by step-wise removal of the sulfates and carbohydrate residues ***(Neufeld and Meenzer, ٢٠٠١).***

There are ١٠ known enzyme deficiency that give rise to six distinct MPS. Most of these enzymes have been extensively purified, their biosynthesis and processing have been elucidated and their primary structure determined from the sequence of the corresponding cDNAs ***(Meenzer, ٢٠٠٣).***

Clinical symptoms eventually result from the lysosomal storage of the partially degraded glycosaminoglycans ***(Scott et al., ١٩٩٥).***

Incompletely degraded glycosaminoglycans accumulate in multiple organ systems leading to progressive worsening of the clinical manifestation. MPS share many clinical features, though in variable degrees. These include a chronic and progressive

course, multisystem involvement, organomegaly, dystosis multiplex and abnormal facts. There is clinical similarity between different enzyme deficiencies and conversely a wide spectrum of clinical severity within any one enzyme deficiency ***(Muenzer, ٢٠٠٣).***

The MPS are inherited as autosomal recessive traits with the exception of the two subtypes of Hunter's disease, which are X-linked recessive ***(Muenzer and Fisher ٢٠٠٣).***

Disorders that result in heparan sulfate storage have progressive central nervous system involvement. Affected patients may have macrocephaly and develop communicating hydrocephalus. Dermatan sulfate storage is associated with progressive visceral and bone involvement. Affected patients may have hepatosplenomegaly, cardiomyopathy or cardiac valvular involvement ***(Muenzer, ٢٠٠٣).***

The cardiac and ocular manifestation are common in Egyptian patients with MPS. So regular cardiac examination, echocardiography and eye examination with slit lamp, fundus examination and regular measurement of the intraocular pressure in patients with MPS is necessary ***(Shawky et al., ٢٠٠١).***

Hurler syndrome or mucopolysaccharidosis type ١ (MPS-١) was one of the first to be described ***(Hurler, ١٩١٩).*** It result from deficient activity of a-L-iduoronidase ***(Scott et al., ١٩٩٥).***

Simple enzyme assays are available for the diagnosis the MPS, prenatal diagnosis following amniocentesis or chorionic villus biopsy is possible for all MPS. ***(Wenger et aL,*** ١٩٩٧***).***

Scott et al.,(١٩٩٥) demonstrated that the IDUA gene spans approximately ١٩ Kb and it split into ١٤ exons. The first ٢ exons are separated by an intron of ٥٦٦ bp; a large intron of approximately ١٣ Kb follows and the last ١٢ exons are clustered within ٤,٥ Kb.

Bunge et al., (١٩٩٤) found that the ٢ common nonsense mutations, W٤٠٢x and Q٧٠x were identified in ٣٧٪ and ٣٥٪ of mutant alleles respectively. He identified ١٣ novel and ٧ previously reported mutations of IDUA, covering ٨٨٪ of mutant alleles and ٨٦٪ of genotypes. In Caucasian population, the mutation trp ٤٠٢-to-ter had previously been identified as a common MPSI mutation.

Supportive management with particular attention to respiratory and cardiovascular complications improve the quality of life for patients and their families. Early diagnosis of mucopolysaccharidosis is important because of the effectiveness of bone marrow transplantation and enzyme replacement therapy as efficient methods of treatment of MPSI before the appearance of manifestations ***(Muenzer,*** ٢٠٠٣***).***