

Clinical Problems in ML II and III: Extra-skeletal Manifestations

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Mucopolysaccharidosis II and III alpha/beta (ML II and ML III) are lysosomal disorders in which the essential mannose-6-phosphate recognition marker is not synthesized onto lysosomal hydrolases and other glycoproteins. The disorders are caused by mutations in GNPTAB, which encodes two of three subunits of the heterohexameric enzyme, N-acetylglucosamine-1-phosphotransferase ML II, recognizable at birth, often causes intrauterine growth impairment and sometimes the prenatal "Pacman" dysplasia. The main postnatal manifestations of ML II include gradual coarsening of neonatally evident craniofacial features, early cessation of statural growth and neuromotor development, dysostosis multiplex and major morbidity by hardening of soft connective tissue about the joints and in the cardiac valves. Fatal outcome occurs often before or in early childhood. ML III with clinical onset rarely detectable before three years of age, progresses slowly with gradual coarsening of the facial features, growth deficiency, dysostosis multiplex, restriction of movement in all joints before or from adolescence, painful gait impairment by prominent hip disease. Cognitive handicap remains minor or absent even in the adult, often wheelchair-bound patient with variable though significantly reduced life expectancy. As yet, there is no cure for individuals affected by these diseases. So, clinical manifestations and conservative treatment is important. This review aimed to highlight the extra-skeletal clinical problems in ML II and III.

Keywords: Mucopolysaccharidosis II and III, Extra-skeletal, Clinical manifestations

Introduction

Mucopolysaccharidosis II and III (I-cell disease and pseudo-Hurler polydystrophy, respectively) are rare genetically related inherited metabolic disorders of lysosomal metabolism with a combined frequency of 1:422,000¹⁾. Mucopolysaccharidosis II and ML III are closely related diseases, first described in the 1960s. These are characterized by disordered processing of multiple lysosomal degradative enzymes caused by the deficiency or abnormal function of UDP-N-acetylglucosamine:lysosomal enzyme N-acetylglucosaminyl-1-phosphotransferase²⁾ The underlying defects result in deficient post-translational modification of numerous enzymes, which depend on mannose phosphorylation for uptake and localisation by cells where substrate degradation occurs³⁾.

ML II has symptoms and signs similar to those encountered in

patients with mucopolysaccharidoses and to a lesser extent gangliosidoses. It is characterised by coarse facial features, short stature, hyperplastic gums, organomegaly, and retarded psychomotor development⁴⁻⁷⁾. In those patients surviving the newborn period, the progressive disorder results in severe learning difficulties, microcephaly, coarse facies, hernias, and a severe skeletal dysplasia. Although some patients survive into the teenage years, the majority die from cardiac or respiratory disease in the first decade of life⁸⁾.

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Intelligence and Brain Problems

Mental retardation of ML II is severe. Mental deficiency in MLIII is in a lesser degree when compared with ML II¹⁰. All ML II patients had delayed and deficient neuromotor development. Nearly all made vocal sounds, but verbal expression remained limited to few words, poorly and hoarsely pronounced. Cognitive development and receptive language skills fit best into the range of moderate intellectual disability, but formal psychometric testing could not be performed in most patients⁹. Many children with ML III have normal intelligence, with a mean verbal IQ of 83 (range 71–100), nonverbal IQ of 83 (range 71–103), and composite IQ of 81 (range 67–96). But some may have learning disabilities. Some individuals with ML III suffer from obsessive compulsive disorder, and short-term memory loss later in life has been reported. Children with ML II experience progressive storage of mucopolysaccharides and glycosaminoglycans in the brain leading to the slowing of development by ages 6 months to 2 years, followed by a progressive regression in skills until death⁹.

Respiratory Problems

All patients experienced increased morbidity of recurrent respiratory infections⁹.

Recurrent respiratory infections, including pneumonia, can be occurred. The patient with the most severe tracheomalacia required tracheotomy and tracheal stents. Even among patients without frequent respiratory illness, intubations for surgical procedures were often described as complicated necessitating the use of fiberoptic equipment⁹.

Sometimes the individual may have sleep apnea. There are reports of tonsils and adenoids growing back and continuing to cause airway problems¹⁰.

Dental Problems

Among the oral manifestations found in ML II are gingival and alveolar thickness evolving to open bite. Other findings are delayed tooth eruption, dental impaction, dental hypocalcification, lack of lip seal and accumulation of mucopolysaccharide material at the dental follicle. Sometimes the tongue may be enlarged, and the roof of the mouth may have a high arch. The mouths of children with ML III, on the other hand, are generally normal¹¹⁻¹³.

Cardiovascular Problems

Muscular tissue, including cardiac muscle, is relatively spared; however, significant vacuolization is present in the art's connective tissue cells of the heart valves. This leads to thickening of the valves, which results in clinically significant valvular disease. Children with ML II or III may develop heart disease, but to a very different degree. Those who have ML III may not experience problems until much later in life. In general, the heart will be much more severely affected in children with ML II. Cardiac manifestations reported in the published reports include cardiomyopathy, right and generalized ventricular hypertrophy, valvular thickening, and regurgitation, with the mitral valve, and, less commonly, the aortic valve being the most frequent findings^{5,14-16}. Mitral and aortic valve thickening was the most common problem detected by echocardiography. Hypertrophy of ventricular walls was a consistent feature in the longer surviving patients⁹.

Abdomen and Hernias

A child with ML II is likely to have a protruding abdomen due to posture, weakness of the muscles, and hepatomegaly, rarely splenomegaly. Frequently, hernia can be occurred because of a weak spot in the wall of the abdomen. Individuals with ML III are less likely to have hernias^{10,14,16}.

Skin Problems

Individuals with ML II and III tend to have thickened and tough¹⁰. Excess hair on the face and back occasionally occurs. Sweating and cold hands and feet also are occasional problems, and are possibly related to the heart, circulation or other mechanisms that control temperature regulation. Irritated areas or rashes should be monitored.

Eyes Problems

Children with ML II and III may be affected by corneal clouding. There may be problems with vision caused by changes to the retina or glaucoma (increased pressure) that should be checked during an eye examination. Storage in the retina can result in loss of peripheral vision and night blindness^{4,14,16}.

Ears Problems

Some degree of deafness is common in both ML II and III. It may be conductive or nerve deafness or both (mixed deafness) and may be made worse by recurrent otitis media. It is important that individuals with ML II and III have their hearing monitored regularly so that problems can be treated early to maximize their ability to learn and communicate¹⁴.

Conclusion

There are various extra-skeletal manifestations in ML III and III. As yet, there is no cure for individuals affected by these diseases. Natural history studies are providing comprehensive information about the disease symptoms and management, disease progression and future research opportunities. Treatments are available to manage the challenges and improve the quality of life of individuals affected with ML II and III. From birth or time to diagnosis, early and systematic study of individuals affected with ML II and III is needed. More studies are needed for ML diseases continuously to look for better and more effective ways to treat them.

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