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SHORT REPORT

Effect of discontinuing of laronidase in a patient with mucopolysaccharidosis type I

A. T. Anbu · J. Mercer · J. E. Wraith

Summary We present a patient on enzyme replacement therapy who showed rapid deterioration when laronidase was discontinued owing to pregnancy.

Mucopolysaccharidosis (MPS type I, McKusick 25280) is a chronic, progressive, debilitating and life-threatening lysosomal storage disorder. It is caused by deficiency of the enzyme α-L-iduronidase (IDUA, EC 3.2.1.76), which facilitates the catabolism of the glycosaminoglycans (GAGs) dermatan sulphate and heparan sulphate. A deficiency of IDUA results in GAG accumulation and subsequent damage to the tissues and organs. The clinical manifestations include learning difficulties, facial and skeletal abnormalities, upper airway obstruction, corneal clouding, hepatosplenomegaly, valvular heart disease and joint stiffness. MPS I has a wide spectrum of clinical severity ranging from the most severe Hurler syndrome (MPS IH) through the intermediate Hurler–Scheie syndrome (MPS I H/S) to the milder Scheie syndrome (MPS IS).

If it untreated, the major cause of morbidity and mortality is respiratory insufficiency due to a restrictive pattern of lung disease. Enzyme replacement therapy (ERT) with recombinant α-L-iduronidase (laronidase) has shown to significantly improve the quality of life in children and adults with non-Hurler MPS I. Here we present one of our patients on ERT who showed signs of deterioration once Laronidase therapy was discontinued owing to pregnancy.

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A. T. Anbu · J. Mercer · J. E. Wraith (✉)
Willink Biochemical Genetics Unit Royal Manchester, M27 4HA, Children's Hospital, Manchester UK
e-mail: ed.wraith@cmmc.nhs.uk

Case history

A 21-year-old woman was diagnosed with MPS I H/S at 5 years of age when she presented with hearing impairment, abdominal distension, painful hips, photophobia, features of carpel tunnel syndrome and stiff fingers. Her liver was palpable at 3 cm below the costal margin and radiography of the skeleton revealed dyostosis multiplex. Subsequently she developed corneal clouding and mitral valve stenosis. Her development has been appropriate for age throughout.

She was enrolled in the phase 3, multinational, randomized, double-blind, placebo-controlled ERT trial, followed by an extended period of enzyme replacement. Assessments just before commencing active therapy included a liver edge palpable 8.5 cm below the costal margin, a percentage predicted forced vital capacity (FVC) of 44.9% and a 6-minute walk test distance of 294 m.

She subsequently received weekly infusions of laronidase 100 U/kg per week. After 60 weeks of treatment her percentage predicted FVC had stabilized at 45% of normal and her 6-minute walk test distance had improved to 340 m. Her liver was no longer palpable. Between weeks 80 to 84 she became pregnant and ERT was discontinued as there was uncertainty about safety during pregnancy. Pregnancy proceeded normally until 29 weeks of gestation when she went into spontaneous premature labour resulting in the normal delivery of a healthy, normal female infant weighing 1250 g. We were unable to obtain reimbursement/funding from her local health provider to restart her ERT immediately post delivery and treatment was therefore discontinued. When she was reassessed 24 months after discontinuing therapy, her liver had enlarged back to 8.5 cm below the costal margin, her percentage predicted FVC had fallen to 38% of normal and her 6-minute walk test distance had fallen to 259 m, indicating a significant deterioration as compared to values while on ERT.

ERT was recommenced soon after this assessment and at reassessment after 3 months of treatment her 6-minute walk test distance had improved by 11 m (to 270 m) and her percentage predicted FVC had increased to 42%, indicating a pleasing early response to restarting her therapy.

Discussion

Clinical trials with the use of laronidase (Kakkis et al 2001; Wraith et al 2004) have consistently shown a significant improvement in the predicted percentage FVC and 6-minute walk test distance and a reduction in the liver size. In our patient a temporary discontinuation of laronidase led to a rapid deterioration in clinical condition.

Little is known about the use of laronidase during pregnancy, although previous experience with ERT for other lysosomal storage disorders would suggest there would be no adverse effects on the fetus (Elstein et al 2004). We are uncertain about the cause of the premature delivery in our patient but it is likely to have been related to the underlying MPS.

Laronidase therapy is effective in stabilizing or reversing some of the adverse effects of MPS I; however, the beneficial clinical effects are soon lost if treatment is discontinued.

References

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