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PRENATAL DIAGNOSIS OF METHYLMALONIC ACIDURIA AND PROPIONIC ACIDEMIA

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Propionate metabolic defects may induce propionic acidemia (PA) or methylmalonic aciduria (MMA), which are caused by the deficiency of propionyl CoA carboxylase (PCC) and methylmalonyl CoA mutase (MCM) activity, respectively. Patients with these two inherited autosomal recessive diseases are at high risk of mortality due to metabolic acidosis. Measuring the *in vivo* incorporation of 1-[^{14}C]-propionate into protein are able to detect defects in propionate metabolism. This method has been successfully applied for prenatal diagnosis of both of these diseases. The ability of cultured amniotic cells to incorporate the radioisotope label from 1-[^{14}C]-propionate into trichloroacetic acid insoluble material was determined with simultaneous ^{3}H-Leu incorporation an internal control.

During the past years, we have investigated nine pregnancies at risk of PA and MMA from six families (2 PA and 4 MMA). Two cases, with very low propionate incorporation (13-23 pmol/hr/mg protein) by their amniocytes than that of normal reference (170-530 pmol/hr/mg protein), were diagnosed to be affected with PA in two different PA families. After counseling, the pregnancies were terminated between 20 and 21 weeks of gestation as requested by the families. Both propionate incorporation and PCC activity in the fibroblast cultured from the abortuses confirmed that the fetuses were affected with PA. The other seven cases (risk: 2 PA, 5 MMA) were found with propionate incorporation between 118 and 550 pmol/hr/mg protein by their amniocytes, which indicated that these fetuses were not affected. All of them were born normally without any symptom of the propionate metabolic disorders. These prenatal diagnosis of PA and MMA were all confirmed with GC/MS determination of methylcitrate and methylmalonate in amniotic fluid, respectively, by stable isotope dilution method (Dr. Sweetman, L.A.). Determination of PCC and MCM activities in the cultured amniocytes was also in aid of prenatal diagnosis of PA and MMA respectively. Recently, a fetus at risk of MMA was also prenatally diagnosed as a heterozygote by restriction fragment length polymorphism (RFLP) analysis of DNA extracted from amniocytes using hMCM26b cDNA probe and *Hind* III digestion. The propionate incorporation analysis, determination of PCC and MCM activities, and DNA analysis are expected to be applied on chorionic villi samples for prenatal diagnosis of PA and MMA at earlier stage (8-10 weeks) of pregnancy.

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Key words : Prenatal diagnosis, propionic acidemia, methylmalonic aciduria

Introduction

Propionate metabolic defects may induce propionic acidemia (PA; MIM 232000) or methylmalonic aciduria (MMA; MIM 251000), which are caused by the deficiency of propionyl CoA carboxylase (PCC; EC 6.4.1.3) and methylmalonyl CoA mutase (MCM; EC 5.4.99.2) activity, respectively[1]. Patients with these two inherited autosomal recessive diseases are at high risk of mortality due to metabolic acidosis. Measuring the *in vivo* incorporation of 1-[^{14}C]-propionate into protein is able to detect defects in propionate metabolism[2]. This method has been successfully applied for prenatal diagnosis of both of these diseases.

Materials and Methods

The propionic acidemic and methylmalonic aciduric patients were diagnosed by ketogenic hyperglycinemia and found with characteristic abnormal organic acids in their urine by gas chromatography-mass spectrometry (GC/MS) analysis[3].

The ability of cultured amniotic cells to incorporate the radioisotope label from 1-[^{14}C]-propionate into trichloroacetic acid insoluble material was determined with simultaneous ^{3}H-Leu incorporation an internal control as modified from that used for human fibroblast[2]. The activities of PCC and MCM in the cell lysate were determined by [^{14}C]-CO_2 fixation[4] and high performance liquid chromatography[5] methods, respectively. Stable isotope dilution analysis of methylcitrate and methylmalonate in amniotic fluid[6] were kindly performed by Dr. L. Sweetman, Los Angeles and Dr. C. Jakobs, Amsterdam.

The hMCM26 cDNA probe of MCM[7] was kindly provided by Dr. F. Ledley, Houston.

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