

been described up to 22 and 25 years after the initial operative intervention. Despite the occurrence of metastasis, long-term survival is observed after thyroidectomy. The index patient had a recurrence in other lobe of the thyroid after 4 years of initial presentation and now is disease free for last 2 years.

Formal treatment algorithms have not been established for SETTLE because of the rarity of this tumor; partial thyroidectomy is the current standard of care. However the index case underwent completion thyroidectomy for SETTLE in the thyroid remnant four years after initial lobectomy performed for the same diagnosis. Patients with SETTLE are to be closely followed as multifocality may manifest and be detected later.

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Biliary Atresia and Cytomegalovirus and Response to Valganciclovir

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Biliary atresia has been commonly reported with cytomegalovirus (CMV) infection. CMV positive patients may present with a later onset however long term outcome is similar to non-CMV patients. There are very few case reports of role of antivirals in CMV and biliary atresia. We treated a 2 month old girl with biliary atresia who underwent portoduodenostomy at 2½ months of age but continued to have jaundice (bilirubin = 23.6 mg/dl) even after 1 month of Kasai's surgery and subsequently was treated with valganciclovir for 6 weeks following which her jaundice resolved.

Key words: Biliary atresia, Cytomegalovirus, India, Valganciclovir.

The pathogenesis of biliary atresia is poorly understood. Association with congenital anomalies in some infants suggests genetic factors. Infection with cytomegalovirus (CMV), group C rotavirus and reovirus type 3 has been associated in certain cases and Fischler, *et al.* found ongoing CMV infection in 39% of patients with biliary

atresia [1-3]. CMV positive patients may present with a later onset; however, long term outcome is similar to non-CMV patients [2]. Outcome may also depend on other factors such as age of surgery, bile duct size and presence of liver damage [4]. Though CMV is known to cause neonatal cholestasis, use of antiviral drugs such as ganciclovir and its oral prodrug valganciclovir in patients

with neonatal hepatitis and CMV has been tried in few patients, with generally good outcome [5-7]. We report a child with biliary atresia who underwent portoduodenostomy at 2½ months of age but continued to have jaundice which improved after treatment.

CASE REPORT

A 2 months old girl born of non-consanguineous marriage at full term with birth weight of 2.6 kg presented with jaundice with clay colored stools since birth, increasing pallor and left focal convulsion. There was no fever, altered sensorium or abdominal distension. She was on exclusive breast feeds. On examination, weight was 3.75 kg, length was 54 cms, she had pallor, icterus, tense bulging anterior fontanelle and hepatosplenomegaly. There was no focal neurological deficit. Investigations showed hemoglobin of 6.8 g/dL, white cell count of 9,500/cumm (50% polymorphs, 50% lymphocytes), platelets of 4,25,000/cumm. Her bilirubin was 9.6 mg/dL (direct = 5.1 mg/dL), SGOT was 166 IU/L, SGPT = 106 IU/L, total proteins = 5.3 g/dL, albumin = 2.7 g/dL. Prothrombin time and partial thromboplastin time were more than 2 minutes. Serum ammonia was 190 µg/dL and blood sugar was 68 mg/dL. Serum electrolytes, blood gases and creatinine were normal. CT brain showed right frontal lobe hemorrhage with perifocal edema with mild shift of midline to left side. USG abdomen showed hepatomegaly with non-visualization of gall bladder. She was treated with fresh frozen plasma, blood transfusion and anticonvulsants. Her TORCH titres (sent before blood transfusion was given) showed positive CMV IgM. HIDA scan after a 5 days priming with phenobarbitone and urseodeoxycholic acid showed poor tracer uptake and no excretion even after 24 hours in the intestine. After stabilization of condition, she underwent an intraoperative cholangiogram that confirmed the diagnosis of biliary atresia and a portoduodenostomy was done at 2½ months of age. Liver biopsy at that time showed early cirrhosis with bile ductular proliferation, and biliary channels more than 150 microns. Post-operatively, even at 3½ months of age, she continued to have jaundice (bilirubin = 23.6 mg/dL). Her CMV viral load at that time was 100 copies/mL and ophthalmological examination and hearing test were normal. She was given valganciclovir (250 mg/m²/day) for 3 weeks following which CMV viral load became undetectable, bilirubin decreased to 5.9 mg/dL and liver transaminases decreased. Valganciclovir was then tapered to 125 mg/m²/day and given for another 3 weeks. Currently the child is 2 years, has normal milestones, is seizure-free and off anticonvulsant, has normal liver function tests, no hearing or visual deficit but has umbilical varices. Endoscopy showed no esophageal varices.

DISCUSSION

An association between cytomegalovirus infection and intrahepatic and extrahepatic forms of neonatal cholestasis has been reported in literature [6]. Whether CMV triggers mechanisms that lead to pathogenesis of biliary atresia remains unproven [8]. CMV replicates in both hepatocytes and cholangiocytes during infection and liver damage may be related to direct cytopathic effect or the immune response of the host [9].

Chang, *et al.* have reported that CMV DNA was detected in 46% of babies with neonatal hepatitis and suggested that CMV could play a major role in pathogenesis of neonatal hepatitis [10]. Fischler, *et al.* [8] found that in patients with biliary atresia and CMV, IgM deposits were significantly higher on liver biopsies than in biliary atresia patients without CMV, suggesting that CMV may be triggering immunologic processes causing biliary atresia.

However, treatment of CMV in patients with biliary atresia has not been studied much and its effect on outcome is not known. Increasing number of studies indicate the necessity of treatment, especially in cases with symptoms of acute or chronic cholestatic hepatitis or proven histopathological findings [5-7,9]. Currently, there are four antivirals available for treatment of CMV: ganciclovir, valganciclovir, foscarnet and cidofovir, of which ganciclovir and its oral prodrug valganciclovir have been studied in neonates. Ganciclovir has been used in 2 patients with biliary atresia and CMV, of which one responded [2]. Similarly in our patient, since the child was still passing clay stools even after 1 month of portoduodenostomy and jaundice was still high, a trial of valganciclovir was given in view of detectable CMV viral load. However, whether ganciclovir or valganciclovir will be useful in all patients with biliary atresia and CMV needs to be evaluated in larger studies.

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Permanent Neonatal Diabetes Caused by a Novel Mutation

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Most cases of permanent form of neonatal diabetes mellitus (PNDM) are due to dominant heterozygous gain of function (activating) mutations in either *KCNJ11* or *ABCC8* genes, that code for Kir 6.2 and SUR1 subunits, respectively of the pancreatic β -cell KATP channel. We describe the interesting case of an infant with PNDM, in whom a compound heterozygous activating/ inactivating mutation was found with clinically unaffected parents, each carrying a heterozygous mutation in *ABCC8*, one predicting gain of function (neonatal diabetes) and the other a loss of function (hyperinsulinemia).

Key words: *ABCC8, Activating/ inactivating, Compound heterozygous, Neonatal diabetes, Permanent, Sulphonylurea.*

Permanent neonatal diabetes (PNDM), which refers to onset of diabetes before the age of 6 months with persistence through life, is a rare disorder occurring in one in 0.2-0.5 million live births [1]. Almost all cases of neonatal diabetes (NDM) are of monogenic etiology in contrast to the autoimmune etiology of diabetes presenting in children beyond 6 months of age [2]. Activating mutations in *KCNJ11* and *ABCC8* genes, that encode the Kir6.2 and SUR1 subunits, respectively, of the pancreatic β -cell KATP channel together account for approximately 40% of all cases of PNDM [3].

Mutations in *KCNJ11* and *ABCC8* give rise to two opposing phenotypes of congenital hyperinsulinemia (CHI) and NDM. Loss of function (inactivating) mutations abrogate the channel function, causing CHI while gain of function (activating) mutations impair the ability of ATP to close the channel, causing NDM [2]. While CHI is caused by recessively inherited homozygous mutations, most cases of NDM are caused by heterozygous (dominant) *de novo* mutations.

Recessive inheritance of PNDM is rare and has been described in only 8 patients till date, out of which 3 each had homozygous and compound heterozygous activating mutations of *ABCC8*, respectively [4]. Previously described in only 2 patients [4], with our baby representing the third case, a novel mutational mechanism has been observed in which there is compound heterozygous activating/ inactivating mutation of the *ABCC8* gene, i.e., one allele has a mutation with loss of function effect and the other has a mutation that predicts gain of function.

CASE REPORT

A 4 week old baby boy was diagnosed as diabetes mellitus (with ketoacidosis at onset) at a hospital in Punjab and referred to us at the age of 8 weeks. He was the first born baby of non-consanguineous parents, delivered at term with weight appropriate for dates, with no significant perinatal problems. There was history of diabetes in paternal grandfather and great grandmother. The infant was managed with twice daily injections of NPH insulin