who underwent liver transplantation for urea cycle disorders (UCD, n=39), maple syrup urine disease (n=12), and two organic acidemia (OA) disorders (methylmalonic acidemia (MMA, n=30), and propionic acidemia (PA, n=4)) between 1997 and 2019. **Results:** At the time of transplantation, median age was 1 year (range 0-17 years). Of the 85 patients with UCD, MSUD, and OA: 52 patients (70.6%) received whole liver grafts, 32 patients (32.6%) received partial grafts, and 1 (1.2%) received a split graft. Living donation was used in one patient with citrullinemia. Fourteen patients underwent simultaneous liver-kidney transplantation (SLK) all of whom were transplanted for methylmalonic acidemia (median age at combined SLK was 5 years). Over a mean follow-up period of 6.9 years (range 1-19 years), Of the nine patients (10.6%) that developed graft failure: four were re-transplanted for HAT and two were re-transplanted for chronic rejection (of which one patient underwent a second SLK). Of remaining three patients with graft failure who were not re-transplanted: two had chronic rejection and one had primary non-function (PNF). Six patients (7.0%) died: two from intra-operative cardiac arrest at the time of transplant (one in the setting of hemorrhage and the other from a metabolic crisis), one from infectious complications, one from primary non-function and two from chronic rejection. The intra-operative metabolic crises leading to death, in a patient with MMA, reveals that clinical wellness can be falsely reassuring in this medically fragile population. Secondary to the peri-transplant metabolic crisis, our center instituted standardized protocols for pre-, peri- and post-operative management. Since the institution of this protocol, there have been no subsequent intra-operative deaths in this population. **Conclusion:** We present the largest single center series of children transplanted for qualifying UCDs, MSUD, and qualifying OAs. Transplant evaluation at our center is inclusive of the metabolic genetics team and early referral for transplant evaluation may explain our low median age at the time of transplant to confer neuroprotection for children at risk of recurrent metabolic crises. Incidence of HAT in this population is low, despite use of primarily whole grafts in the smallest children. We report the experience of our center to highlight the importance of multidisciplinary protocols to minimize morbidity and mortality in this population and to continue to ensure excellent post-transplant outcomes.

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★ 1467

PHENOTYPIC DIVERGENCE OF JAGGED1 AND NOTCH2-ASSOCIATED ALAGILLE SYNDROME: RESULTS FROM THE INTERNATIONAL MULTICENTER GALA STUDY GROUP

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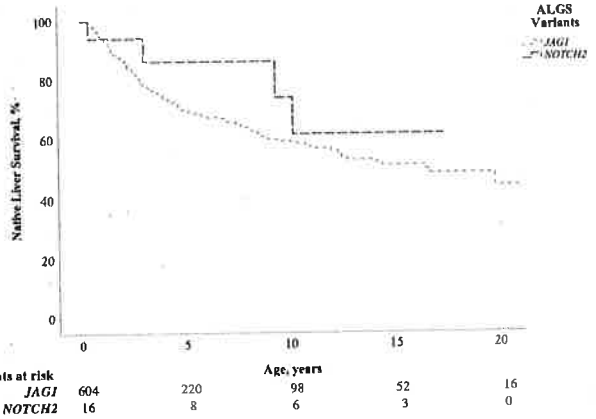
Background: Alagille Syndrome (ALGS) is an autosomal dominant disorder caused by pathogenic variants in *JAGGED1* (*JAG1*) or *NOTCH2*, and is typically associated with cholestasis and congenital heart disease. While the phenotype of *JAG1*-associated ALGS has been reasonably well characterized, *NOTCH2*-associated disease has only been reported in a small number of individuals. The Global ALagille Alliance (GALA) Study Group has ascertained the largest genetically confirmed ALGS cohort to date, allowing characterization of the *NOTCH2*-associated phenotype. **Methods:** This was a retrospective, international, multicenter study collecting data on ALGS children born between Jan-1997 and Aug-2019 with a pathogenic or likely pathogenic variant in *JAG1* or *NOTCH2*. The pathogenicity of variants was classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Clinical characteristics between *NOTCH2*- and *JAG1*-ALGS patients were compared using Chi-square test or Fisher's exact test, as appropriate. Native liver survival (NLS) and overall survival rates were calculated using the Kaplan-Meier method and differences between the groups were compared using log-rank test. **Results:** Nineteen (79% male) *NOTCH2* patients and 755 (57% male, p=0.05) *JAG1* patients were identified. Pathogenic *NOTCH2* variants included frameshift (32%), missense (26%), splice site (21%) and nonsense (21%). *NOTCH2*- and *JAG1*-ALGS patients were similar in terms of neonatal cholestasis (89% vs. 82% respectively, p=0.55), histological evidence of bile duct paucity (42% (n=5/12) vs. 60% (n=186/308), p=0.24), and presence of renal anomalies (26% vs. 34%, p=0.46). However, *NOTCH2* patients were significantly less likely to have characteristic facies (53% vs. 88%, p<0.001), an ECHO-confirmed cardiac anomaly (58% vs. 93%, p=0.001), posterior embryotoxon (14% vs. 53%, p=0.004), or butterfly vertebrae (0% vs. 44%, p=0.001). 10- and 18-year NLS in patients presenting with neonatal cholestasis were comparable between the two groups (59% and 74%; 48% and 62%, respectively; log-rank p=0.31). Overall survival rates at 10-and 18-years were ≥90% in both groups (log-rank p=0.71). **Conclusion:** We describe the largest cohort of *NOTCH2*-associated ALGS patients. *NOTCH2*-ALGS patients exhibit significantly reduced penetrance of extrahepatic features when compared to *JAG1*-ALGS patients. Since all patients were ascertained from liver clinics there is a bias in favor of liver involvement, however the presentation of liver disease, rates of NLS and overall survival outcomes were comparable among *NOTCH2*- and *JAG1*-ALGS patients. These data suggest that reliance on classical clinical phenotypic definitions of ALGS may miss patients with *NOTCH2*-related disease and that genetic testing is crucial for diagnosis. Further investigation will be necessary to determine if additional "non-ALGS" clinical features are present in patients with *NOTCH2* mutations.



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Jesus Quintero Bernabeu – Alexion Pharmaceuticals, Inc.: Consulting

Nanda Kerkar – High Tide: Advisory Committee or Review Panel

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Richard J. Thompson – Albireo Pharma: Consulting; Mirum Pharma: Consulting; Generation Bio: Consulting; Qing Therapeutics: Consulting; Alnylam: Consulting; Rectify Therapeutics: Consulting; Sana Biotechnology: Consulting; EVOX Therapeutics: Consulting; Retrophin: Consulting

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PROSPECTIVE FIBROSCAN® MEASUREMENTS OF OBESE CHILDREN WITH AND WITHOUT AN INITIALLY ELEVATED ABNORMAL ALANINE AMINOTRANSFERASE (ALT) IDENTIFIES A CRITICAL ROLE FOR ALT IN IDENTIFYING ADVANCED FIBROSIS GROUP

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Background: Nonalcoholic fatty liver disease (NAFLD) has rapidly become the most common form of chronic liver disease in children and adolescents. Abnormal elevations in aminotransferases are commonly used to identify those children who may have more active inflammation, but the possibility of missing advanced disease could be occurring in those who have initially normal levels and subclinical disease activity. Vibration controlled transient elastography using the Fibroscan® device can detect liver steatosis and fibrosis non-invasively. We used Fibroscan® to look for hepatic steatosis and fibrosis in obese children with and without an abnormally elevated ALT to assess the utility of this biomarker as a screening test for more advanced liver disease. **Methods:** All obese subjects (BMI≥30) with abnormal ALT (twice above ULN ≥50 U/L for boys and ≥44 U/L for girls) and normal ALT (twice below ULN, < 50 U/L for boys and < 44 U/L for girls) were prospectively enrolled. Both male and female obese subjects of all races/ethnicities, and age between 8-21 years were included. **Results:** A total of 153 subjects (96 in the normal ALT group, and 57 in abnormal ALT group) were enrolled. White race was predominant (73%) followed by Hispanics (18.9%) and African-Americans (4.5%). Fibroscan® readings in the two groups were compared. In the abnormal ALT group, where more advanced disease was expected, 28% subjects had advanced fibrosis and 26.3% had cirrhosis. In comparison, in the normal ALT group, only 7.2% subjects had advanced fibrosis and none had cirrhosis (p <0.0001). Similarly, in the elevated ALT group 91.2% subjects had grade III steatosis vs 38.5% subjects in the normal ALT group. **Conclusion:** In a prospective study using non-invasive Fibroscan evaluations over a year time period, the ALT was found to be an excellent biomarker for differentiating more advanced liver disease in this cohort of obese children. Based on these findings and as clinical strategy, regular monitoring of the serum ALT in obe children is suggested, followed by Fibroscan® measuremer once their ALT becomes elevated.

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Nanda Kerkar – High Tide: Advisory Committee or Review Panel

The following people have nothing to disclose: Imdad Ullah, Lawrer Saubermann, Rishi Gupta, Gopal A. Ramaraju

★ 1469

THE PRESENCE OF A TRUNCATING MUTATION IN ABCB11 ABROGATES THE BENEFICIAL EFFECT OF A RESIDUAL FUNCTION MUTATION ON THE COURSE OF SEVERE BILE SAL EXPORT PUMP DEFICIENCY

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