

# Early Diagnosis and Prevention of Hyperbilirubinemia and Autism Spectrum Disorder

There are countless communication proving a strong connection between the neonatal hyperbilirubinemia and autism spectrum disorders.<sup>[1]</sup> Much less communication claims their contrary.<sup>[2]</sup>

## OUR BASIC IDEA

During long-term follow-up studies (3–36 years –  $n = 550$ ), we found only 1 patient suffering from autism spectrum disorder (ASD) in the children and adults who were treated with D-PA in their neonatal period (“New Prevalence Numbers for 2016: 1 in 36 US Children have autism”).<sup>[3]</sup> A 30-year-old male patient was born as a premature infant and had a serious hyperbilirubinemia. He was treated with D-PA without success because exchange transfusion was necessary to perform. It was recommended by us,<sup>[4]</sup> that all newborns should be screened for ASD, particularly the premature babies and infants suffering from hyperbilirubinemia. Presumably, hypercupriuria is found in all neonates since they have the similar metabolism of copper as the patients suffering from Wilson’s disease (WD).<sup>[5]</sup> Investigation of WD and obstructive liver disease using a 24-h urine specimen and penicillamine challenge test to measure the excreted copper/day. Unfortunately, the reference values for neonates are not established yet.<sup>[6]</sup> Although the 24-h urine copper test is inconsistent in the neonatal period, the penicillamine challenge test<sup>[7]</sup> has proved itself to be useful in the detection of high copper in the urine of newborn infants too. First of all, it is important to know the normal copper excretion/24 h in the 2–4 days of life. Soon after it is reasonable to perform the challenge of detecting the expectable hypercupriuria. If the excretion of copper is significantly greater than the standard value, it is suspicious for ASD, and 4–6 days D-PA-treatment may be necessary, especially as this type of chelation therapy beneficial in the treatment and prevention of bilirubin-induced neurologic dysfunction (BIND) and retinopathy of prematurity (ROP) as well. During the past 40 years, neonatologists working in Hungary and the rest of the world<sup>[8,9]</sup> administered D-PA to prevent or treat neonatal hyperbilirubinemia and ROP (at that time - 70s–80s years - the intravenous preparation was available) (metalcaptase<sup>R</sup> - Knoll AG; West-Germany). Hence, all prematures have received

IV - therapy. Only a few term infants were treated orally (300 mg/kg/bw daily for 4–6 days - + 50 mg/kg/bw for the end of 2 weeks to very low birth weight infants WLBW). It is important to note that there was no intolerance or short- or long-term toxicity of the medication, in spite of the fact that D-PA was used 10–20 times higher doses in the newborn period, than those in adult age.

## Our potential joint program

It would be reasonable to measure the excreted copper using a 24-h urine test and detect the serum copper and ceruloplasmin in the cord blood: (1) If the mother blood group is “0,” (2) when the cord bilirubin concentration is high (these babies are jeopardised for both hyperbilirubinemia and ASD!). Kelsey *et al.*<sup>[10]</sup> have supported the usefulness of measuring umbilical cord bilirubin concentration, with scientific evidence. This research work is important for us because it joins our novel concept of the prevention of BIND and ASD.

Our concept may help to answer some of the unsolved questions and concerns occurred in the etiology and pathomechanisms of BIND and the other neurodevelopmental disorders.

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**How to cite this article:** Lakatos L. Early Diagnosis and Prevention of Hyperbilirubinemia and Autism Spectrum Disorder. *Clin Res Pediatr* 2018;1(1):1-2.