



Case Report

Phenylketonuria with Autism Spectrum Disorders- A Case Study

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ABSTRACT

Infantile autism is behaviorally defined as neurodevelopment disorder, beginning at a very young stage in children. The cause of autism remains largely unknown as it is likely multifactorial, arising from the interaction of biologic, genetic and environmental factors. The specific role of neurometabolic abnormalities in autism is largely unknown. But current research may provide insight into the pathophysiologic underpinnings of autism. Our current understanding of autism suggests that it is neurometabolic disorder and that it may be caused by Phenylketonuria, one of the particular enzyme defects. We identified a case report of Phenylketonuria disorder patient having an autistic behavior. We have also recommended Phenylalanine restricted diet for this case. While good care and early intervention can help preventing the progress of mental and developmental disorders associated with the metabolic disorder and need for future research aimed at understanding the relations among autism and neurometabolic disorders.

Key Words: Autism spectrum disorders, Phenylketonuria, HPLC.

INTRODUCTION

Leo Kanner first described autism in 1943. A small group of children who demonstrated extreme aloofness and total indifference to other people. Additionally, the children made little eye contact and had severe language deficits associated with the apparent lack of desire to communicate. They reacted to the environment in very unusual ways and demonstrated no pretend or imaginative play. ^[1] The term “infantile autism” first appeared as a diagnostic label in the Diagnostic and Statistical Manual of Mental Disorders (DSM), Third Edition. The Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association includes five different disorders

under an umbrella term of pervasive developmental disorders (PDDs). ^[2] These include autistic disorder, Asperger’s disorder, pervasive development disorder not otherwise specified (PDDNOS), Rett syndrome, and childhood disintegrative disorder (CDD). In India, while there are no reliable figures available. ^[3]

Autism is a behavioral syndrome with still poorly understood etiologies. Autism is similar to other neurodevelopment disabilities, are generally not “curable” and chronic management is required. Although, outcomes are variable and has specific behavioral characteristics change over time. Most children with ASDs remain within the spectrum as adults and regardless of their

intellectual functioning, continue to experience problems with independent living, employment, social relationships, and mental health. [4] In most cases, it is probably caused by multifactorial inheritance that means the association of genetic factors to environmental factors. On the other hand, in 10 to 20% of all cases a specific cause can be determined, including chromosomal abnormalities, metabolic disorders, food allergy, monogenic conditions like tuberous sclerosis, fragile X syndrome or other entities, as well as “pure” environmental factors. [5]

There are many neurometabolic disorders with an autistic phenotype. These include phenylketonuria (PKU), disorders of purine metabolism, biotinidase deficiency, disorders of cerebrospinal fluid (CSF) neurotransmitters such as deficiencies of folic acid, Smith-Lemli-Opitz syndrome (SLOS), Creatine deficiency, mitochondrial disorders and others. [6] These are rare disorders that are typically inherited in an autosomal recessive fashion and generally present within the first 3 years of life. Concerning the metabolic disorders, phenylketonuria (PKU) was frequently associated with autistic symptoms. [7]

Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (Phe) metabolism associated with deficient activity of Phenylalanine hydroxylase (PAH) and elevated concentrations of Phenylalanine and Phenylalanine metabolites. Untreated PKU is characterized by severe to profound IQ problems, intellectual disability, mental retardation, seizures, autistic-like behaviors, microcephal, rashes, hypopigmentation, and a musty body odor (phenyl acetic acid), altered brain development and an autism phenotype. Phenylketonuria (PKU) was frequently associated with autistic symptoms. This association has almost vanished since the introduction of early

detection and treatment for phenylalanine hydroxylase (PAH) deficiency. The possibilities that dopamine deficiency is common to autism and poorer control PKU. [8]

Hyper phenylalaninemia may be defined as having a blood Phenylalanine concentration above the reference range (20-130 umol/L depending on age). Different schemes exist for classifying subtypes of PKU on the basis of the severity of the clinical or biochemical and/or molecular phenotype. Patients have been classified as having moderate hyperphenylalaninemia if their blood Phenylalanine concentration without dietary therapy is elevated but less than 200 umol/L (10 mg/dL). Significant PKU is characterized by a Phenylalanine concentration higher than 200 umol/L (20 mg/dL) while receiving a normal dietary intake of protein. In rare cases, an elevated blood Phenylalanine concentration may be caused by inherited disorders of the biosynthesis or recycling of tetrahydrobiopterin (BH4), a cofactor in the PAH reaction. [9] Phenylketonuria individuals presenting with neurological impairments including autistic behavior still occur.

CASE REPORT

A Male, 6 years old, 1st child of the family was brought by his parents. The parents denied consanguinity. The family history was otherwise unremarkable. Pregnancy was uncomplicated and birth was at term by a normal vaginal delivery. Neonatal screening was not performed. His development was globally delayed and he never acquired verbal language. His neuromotor development was globally delayed. There was no history of seizures. He would not make meaningful eye to eye contact even when the family member tried to do so. Patient was vaccinated and his hair was brown in colour. He had complaints

with hypertonic, microcephaly, mousy body odor, onset, pigmentation, skin and sclera, seborrheic skin rash.

The blood and the urine sample of the subject were tested for inborn errors of metabolism, which involves the amino acids, organic acids, carbohydrates, ketones and carnitine were measured quantitatively. We used HPLC (Shimadzu LC 20AD) with a Diode array detector (SPD M20A) for quantization of amino acids. We followed the instruction in Pico, Tag amino acids kit (Waters, Water Corporation, USA) for mobile phase, standard and sample preparation, www.waters.com. Amino acid was quantitated using the Phenylisothiocyanate method on the HPLC using a C-18 waters (150x4.6mm, particle size 5µm) column. The column temperature was 46°C for the determination of Amino acids. Flow rate was set to 1.0 ml/minute and detection was at 254nm. The injected volume was 20 µl. Plasma amino acids studies revealed the significantly elevated levels of Phenylalanine. The Phenylalanine levels found to be increased to 570 umol/L (Normal range 20-130 umol/L). Presence of phenylalanine was confirmed by co-elution with standard Phenylalanine. The elevated levels of phenylalanine indicate towards a possible phenylalanine metabolism related disorder.

In the index case Phenylalanine level was very high. He was referred to a nutritionist. The nutritionist concluded that the benefit could be substantially provided by a phenylalanine-restricted diet for late-diagnosed mentally retarded with phenylketonuria. [10] Phenylalanine restricted diet was purchased from Mead Johnson, USA. In the context of the present study, the Phenylalanine content of the diet was initially established at 1000 mg per day and was then reduced to 900 mg after three months, thereby ensuring good control of Phenylalanine blood level. The diet

essentially consists of fruits, vegetables and grain products. Special products low in Phenylalanine (e.g. bread, pasta, broth) was also used. An appropriate supply of Phenylalanine-free proteins and tyrosine was ensured by the consumption of special beverages and tyrosine is an essential by-product of Phenylalanine. Patient was put on a diet at the age of 6. He is now 11 Years of age and is still continuing the diet and his Phenylalanine levels are monitored every year.

The phenylalanine levels slowly decreased and phenylketoacids were elevated. Recently, we monitored his Phenylalanine levels. It was 190umol/L. During this period of the 5 year study, the family reported some improvement in behavior, milestones and sleep. No other improvements are reported. He showed signs of hyperactivity at the age of 9. In conjunction with symptoms stated earlier, a suspicion of an autism spectrum disorders was made. He was then directed to a clinical psychologist who diagnosed him to have autism spectrum disorders after assessments by DSM-IV-TR criteria. PKU diet was continued for controlling the phenylalanine levels in the blood and advised constant medical and psychological treatment in the form of occupational, physical and speech therapy to manage medical and behavioral problems.

DISCUSSION

The child in this case study presented with the Phenylketonuria with autism behaviour. The constellation of symptoms pointed towards autism behavior. In our view, patient recovery from autistic disorders is unexpected and unexplained. There exists is no specific treatment for autistic disorders. Early Investigation and dietary treatments for PKU has allowed vast improvements in the IQ, psychological and behavioral outcomes of PKU. It is important

for clinicians to be aware of ASDs being related to PKU disorder because increased identification will help in greater understanding of these disorders and proper guidance will help the patient and family to reduce the burden on the parents and patient himself/ herself. The literature on the outcome of PKU treatment supports the conclusion that outcome in PKU is related to the concentration of Phenylalanine in the blood of affected individuals, especially in the first 3 years of life. Although there is not a consensus in the literature, the trend is toward supporting a concentration of Phenylalanine in the blood that is not below the bottom of the normal range and does not exceed. The primary goals of PKU investigation and treatment are to minimize the core features and associated deficits, maximize functional independence and quality of life.

Interest in studying these rare cases is increasing, not only because proper diagnosis is important to a given patient but also because these cases may be able to provide clues to the underlying metabolic abnormalities in idiopathic autism. The follow-up improvement in the child is promising in the case of many such affected children, who may go undiagnosed if not screened for an inborn error of metabolism. Any case with presentation of seizures, IQ problem, delayed development and abnormal behavior should be screened for this class of disorders. In our case, no improvement in hyperactivity or speech was noticed. Early treatment of PKU by appropriate dietary restrictions has greatly reduced the prevalence of autism behaviours in affected children and may also improve the autistic phenotype in this population. However, the case study did not show any effect of the Phenylalanine restricted diet on behavior and need for future comprehensive research aimed at understanding the

relations among autism and neurometabolic disorders.

REFERENCES

1. Bauman, ML. 2010. Medical comorbidities in autism: challenges to diagnosis and treatment. *Neurotherapeutics*. (3):320-7.
2. Bilder, Judith Pinborough-Zimmerman, Judith Miller and William McMahon. 2009. Prenatal, Perinatal, and Neonatal factors associated with autism spectrum disorders. *Deborah Pediatrics*. 123: 1293-1300.
3. Chiappedi, M. Rossi, G. Rossi, M. Bejor, M. and Balottin, U. 2010. Autism and classification systems: a study of 84 children. *Ital J Pediatr*. Jan 29:36:10.
4. Chris Plauché Johnson, Scott, M. 2007. Myers and the Council on Children with Disabilities. Identification and Evaluation of Children with Autism Spectrum Disorders. *Pediatrics*. 120: 1183-1215.
5. Nassim Zecavati. and Sarah Spence, J. 2009. Neurometabolic Disorders and Dysfunction in Autism Spectrum Disorders. *Current Neurology and Neuroscience Reports*. 9:129–136.
6. Sempere, A. Arias, A. Farré, G. García-Villoria, J. Rodríguez-Pombo, P. Desviat LR. Merinero, B. García-Cazorla, A. Vilaseca, M.A., Ribes, A. Artuch, R. and Campistol, J. 2010. Study of inborn errors of metabolism in urine from patients with unexplained mental retardation. *J Inher Metab Dis*. J. 33:1–7.
7. Bahare Azadi. Arshia Seddigh. Mehdi Tehrani-Doost. Javad Alaghband-Rad. and Mahmoud Reza Ashrafi. 2009. Executive dysfunction in treated Phenylketonuria patients.

- European Child & Adolescent Psychiatry. Volume 18, 360-368.
8. Miladi, N. Larnaout, A. Kaabachi, N. Helayem, M. and Ben Hamida, M.J. 1992. Phenylketonuria: an underlying etiology of autistic syndrome. A case report. Child Neurol. 1:22-3.
 9. Baieli, S. Pavone, L. Meli, C. Fiumara, A. and Coleman, M. 2003. Autism and phenylketonuria. J Autism Dev Disord. 33(2):201-4.
 10. Eric dion. marie-josée prévost. sylvie carrier. chantal babin. and jacques goisneau. 2001 Phenylalanine restricted diet treatment of the aggressive behaviours of a person with mental retardation. The British journal of developmental disabilities. 47: 221-29.

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