Original Article

The Spectrum of Inherited Gray Matter Degenerative Brain Disorders (DBD) in Children: A Single-Center Study

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Abstract

Objectives: To study the clinical spectrum of inherited gray matter degenerative brain disorders (DBD) in children. **Methods:** This cross-sectional study evaluated children up to 12 y of age, diagnosed with an inherited gray matter DBD in a tertiary care pediatric hospital between July 2019 and December 2020. **Results:** A total of 314 children with progressive neuroregression were screened. Of these, 117 children with inherited gray matter DBD were included in the study. The clinic-based prevalence of DBD was 8.2%, and inherited gray matter DBD was 3.1%. The proportion of the inherited gray matter DBD was 37.3% among the overall DBD cases. Children were categorized into three groups based on the age at onset of disease: below 2 years (N = 57, 48.7%), between 2 and 5 years (N = 32, 27.3%), and between 6 and 12 years (N = 28, 23.9%). Based on the predominant cerebral structure involved, gray matter DBD were classified as cerebral gray matter disorders (53%), basal ganglia disorders (34.1%), and cerebellar disorders (12.8%). Overall, the most common disorders were Wilson disease (18%), neuronal ceroid lipofuscinosis (NCL) (17%), and neurodegeneration with brain iron accumulation (NBIA) (16%). The most common gray matter DBD in children <2 years of age were NBIA (n = 11), Rett syndrome (n = 11), and gangliosidoses (n = 10). NCL (n = 14) and ataxia telangiectasia (n = 6) were most common in the age group of 2–5 years. Wilson disease (n = 19) was the most common disorder in the age group of 6–12 years followed by NCL (n = 4) and NBIA (n = 3). **Conclusion:** Our study highlights the burden and spectrum of gray matter DBD in children. The clinic-based prevalence of DBD was 8.2%, and of inherited gray matter DBD was 3.1%. The proportion of inherited gray matter DBD was 37.3% among the overall DBD cases. Wilson disease, NCL, and NBIA are the most common gray matter DBD in children. Timely diagnosis is important for the prevention of recurrence in subsequent pregnancies.

Keywords: Children, gray matter disease, neurodegeneration, neuronal ceroid lipofuscinosis, neurological deterioration, progressive intellectual, Wilson

Introduction

Degenerative brain disorders (DBD) are characterized by progressive loss of structure or function of specific populations of neurons or their connections, resulting in progressive neurological impairment, for more than 3 months, and include both acquired and inherited causes.[1] They are often classified on the basis of lesional topography into gray and white matter disorders.[2] Gray matter disorders can involve the cerebral gray matter, basal ganglia, brainstem, or cerebellar nuclei. The DBD have also been classified into neonatal, early infantile (between 1 and 12 months of age), late infantile (between 1 and 4 years of age), juvenile (between 5 and 15 years of age), and adolescent-onset disorders based on the age at presentation.[3] The prevalence of diseases causing pediatric DBD varies from 0.1 to 0.6 per 1000 live births.[4,5] The real burden of DBD in India remains unknown.

Despite emerging research in pediatric DBD, there is no universally agreed classification due to the heterogeneous pathomechanisms and evolving molecular basis of these disorders. In a registry-based epidemiological study from UK, nearly half of the children with DBD had a gray matter DBD and 80% of them had disease onset before 5 years of age.[3] In the first year of life, DBD commonly present with microcephaly, neuromotor regression, epilepsy, and tone changes. The clinical presentation in later years is more variable. Although case reports or case series pertaining to specific types of gray matter DBD have been reported from India, there is paucity of studies looking at the overall spectrum of DBD in children. Hence, we planned this hospital-based study to describe the burden and spectrum of inherited gray matter DBD in children.

Material and Methods

This cross-sectional study was conducted between July 2019 and December 2020 in the Department of Pediatrics of a tertiary care pediatric hospital. The study was approved by the

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Institute Ethics Committee. Consecutive children registered in the Pediatric Neurology Clinic with a diagnosis of DBD were screened. Additionally, medical records and case sheets of all children with a diagnosis of DBD in the past 5 years were retrieved from the hospital records for screening. Children of either gender, between birth and 12 years, and diagnosed with a gray matter DBD were enrolled in the study. The diagnosis of DBD was based on the classical clinico-radiological pattern, often supplemented with a biochemical, enzymatic, or genetic corroboration. Children with acquired neuroregression, infections, and nutritional deficiencies were excluded. Demographic and clinical details were recorded in a pre-structured proforma.

Statistical analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 22.0 for Windows). Mean and median were calculated for all quantitative variables. For measures of dispersion, standard deviation or interquartile range (IQR) was calculated. Qualitative or categorical variables were described as frequencies and proportions.

Results

During the study period, 3823 patients were registered in Pediatric Neurology clinic and 314 children fulfilled the criteria of DBD. Of these, 117 children with inherited gray matter DBD were included in the study. The other types of DBD involved the white matter (N = 118, 37.5%), acquired gray matter DBD (N = 43, 13.7%), and uncharacterized DBD/etiology under investigation (N = 36, 11.5%) [Figure 1a and b]. The clinic-based prevalence of DBD was 8.2%, and inherited gray matter DBD was 3.1%. The proportion of the inherited gray matter DBD among the DBD cases was 37.3%. There was a slight female preponderance (n = 60, 51.3%); the male: female ratio was 0.9:1. Figure 2 shows the methodological flow chart and the spectrum of various disorders included in this study.

The median age of onset of neurological symptoms was 2.5 y (IQR 0.8–5). The median age of presentation to the health facility was 6 y (IQR 3–9). The median delay in seeking health care was 2 y (0.7–4 years). Parental consanguinity was observed in 12 (10.3%) and history of affected siblings was noted in 28 (23.9%) cases. In the infantile group, developmental delay (59.6%), tone abnormalities (57.9%), neuromotor regression (52.6%), microcephaly (47.4%), and epilepsy (36.8%) were the predominant presenting features. The children in the late-infantile group presented with regression of milestones (60%), movement disorder (51.8%), seizures (45.2%), cerebellar ataxia (41.9%), and vision impairment (30%). In contrast, the majority of children in the juvenile group presented with tone abnormalities (89.3%), movement disorder (72.4%), speech disturbances (71.4%), cerebellar signs (42.9%), and extrapyramidal symptoms (35.7%).

The majority (76%) of the cases present before the age of 5 years. An age-based classification of gray matter DBD is presented in Figure 3a-c. The most common disorders were neurodegeneration with brain iron accumulation (NBIA) and Rett syndrome in children below 2 years of age, neuronal ceroid lipofuscinosis (NCL), and ataxia telangiectasia (AT) in children 2–5 y of age and Wilson disease in children 6–12 y of age. Based on the topographical classification [Figure 2], gray matter DBD were also classified as disorders of cerebral gray matter (n = 62, 53%), basal ganglia (n = 40, 34.2%), and cerebellar diseases (n = 15, 12.8%). The most common DBD affecting the cerebral gray matter were NCL (n = 20/62, 32%), Rett syndrome (n = 13/62, 20.9%), gangliosidoses (n = 10/62, 16.1%), mucopolysaccharidoses (n = 4/62, 6.4%), early infantile epileptic encephalopathy with neurodegeneration phenotype (n = 4/62, 6.4%), and Menkes disease (n = 3/62, 4.8%). The most common DBD involving the basal ganglia were Wilson disease (n = 21/40, 52.5%) and NBIA (n = 19/40, 47.5%). The most common cerebellar disorders were AT (n = 13, 86.7%) and spinocerebellar ataxia (n = 2, 13.3%).

Discussion

DBD are a significant cause of chronic morbidity and mortality in children. Our study highlights the burden of DBD and inherited gray matter DBD in children at a tertiary care hospital. The clinic-based prevalence of DBD and inherited gray matter

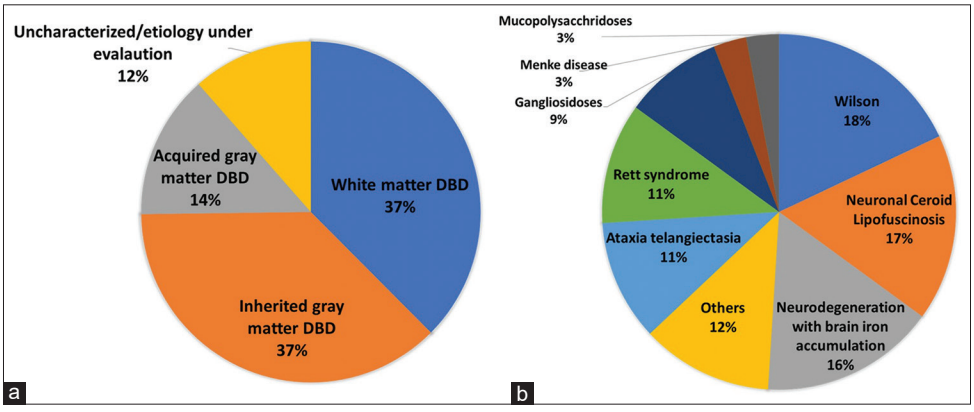

Figure 1: (a and b) The distribution of DBD (a) and inherited gray matter DBD (b) in children in the study

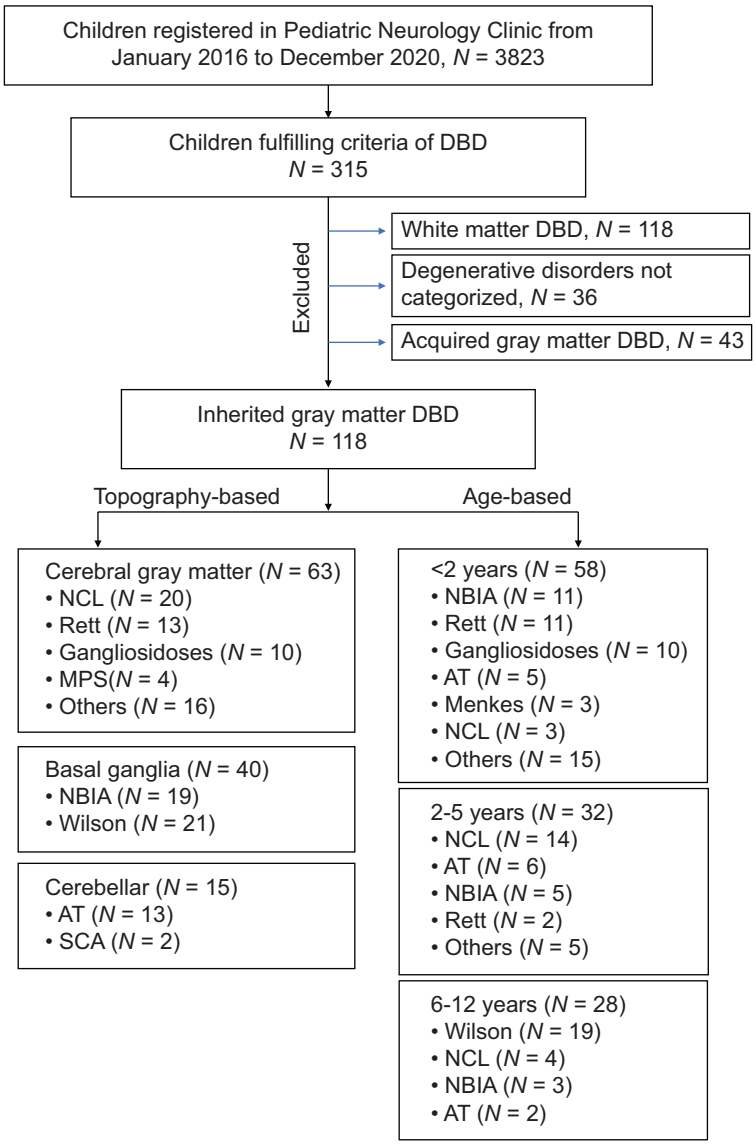

Figure 2: Flowchart of the study (AT: ataxia telangiectasia, MPS: mucopolysaccharidoses, NCL: neuronal ceroid lipofuscinosis, NBIA: neurodegeneration with brain iron accumulation, SCA: spinocerebellar ataxia, others = multiple sulfatase deficiency, Niemann–Pick disease, Gaucher disease, congenital disorder of glycosylation, sulfite oxidase deficiency, *KCDT7*-associated progressive myoclonic epilepsy, Huntington disease, and *FOXG1*-related syndrome)

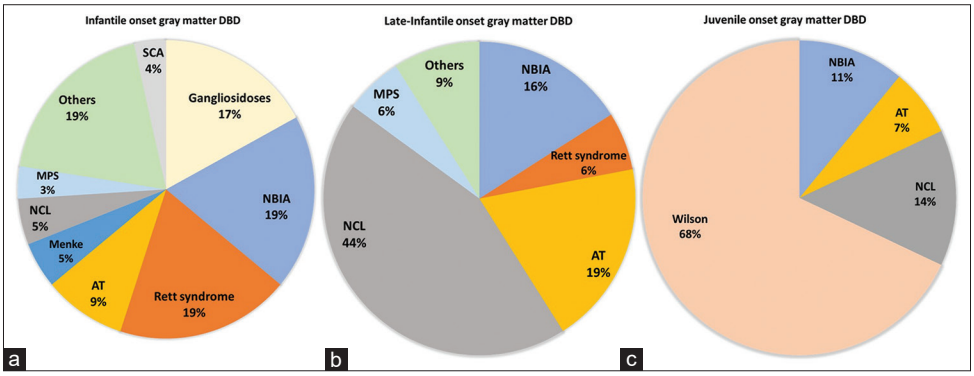

Figure 3: (a-c) Distribution of inherited gray matter DBD based on the age of onset (AT: ataxia telangiectasia, MPS: mucopolysaccharidoses, NCL: neuronal ceroid lipofuscinosis, NBIA: neurodegeneration with brain iron accumulation, SCA: spinocerebellar ataxia

DBD was 8.2% and 3.1%, respectively. In similar studies from resource-limited settings, 1.6% of children attending the pediatric neurology clinic over 10 years[6] and 5.2% of children admitted in the pediatric neurology wards[7] were diagnosed

as DBD. There are a handful of studies on neurodegenerative disorders, but most of them are from developed countries and are based on registry-based population surveillance reporting on the lifetime risk of having a disease-causing DBD.[4,8,9] The proportion of inherited gray matter DBD in these studies ranges from 47 to 51%.[3,8] In our study, inherited gray matter DBD constituted 37.3% of DBD cases. The reasons for heterogeneity in the studies are probably related to the expertise at the individual centers, availability of testing facilities, research interests of the collaborating groups, and the population studied. Additionally, in the absence of a universally accepted case definition for DBD, several disorders including neurometabolic and infections are often included under this umbrella term, making the study population quite diverse. Although prevalence of specific DBD has been reported from India, there is a dearth of studies on DBD as an entity. A study from South India looked at the prevalence of cerebral lipidosis in children with progressive neurodegeneration and showed that sphingolipidosis contributed to 7% of cases among the 771 cases of neurodegenerative disease.[10] Another study determined the prevalence of lysosomal storage disorders (34.8%) in children with neuroregression.[11] Hence, a universally acceptable definition of DBD needs to be formulated that can used uniformly for data collection across regions. With increasing availability of clinical expertise from pediatric neurologists and geneticists, and better diagnostic facilities, better characterization of DBD is expected. Population-based, multi-centric studies and national registries are warranted to identify the true burden of these rare disorders.

The age-based classification of neurodegenerative disorders is a pragmatic one and helps in forming a clinical approach to the cases. It is often not reported in the studies on DBD.[9,12] We followed this approach as it helps in stratifying the etiologies and making a differential diagnosis. Three-fourth of the children in our study presented before the age of 5 years, and almost half of them had an infantile onset. Similar observations have been made by studies from UK and Australia where 46–80% of children with DBD presented before the age of 5 years.[4,8] The variability in the data could be determined by the type of disorders studied under DBD and availability/use of diagnostic services. The most common disorders in the infantile and late-infantile onset groups in our study were NCL, NBIA, Rett syndrome, AT, and gangliosidoses. The UK cohort shows a similar preponderance of NCL, gangliosidoses, mucopolysaccharidoses, and Rett syndrome in this age group, when inherited white matter and mitochondrial disorders are excluded.[4] There is an underrepresentation of NBIA group in older studies,[9,12] and this heterogeneous group is being increasingly recognized by genetic confirmation in children and adolescents. NCL is considered the most common cause of dementia in children and the disorder can present across all age groups.[13] Its preponderance has been seen across all the studies, highlighting the need to recognize its varied manifestations in children.[9,12,14] In comparison, other lysosomal storage disorders such as gangliosidoses and mucopolysaccharidoses were disproportionately less in our study in the older age groups as compared to the western literature. One of the reasons is that we enrolled our cases from the Pediatric Neurology clinic and children with storage disorders without neurological manifestations often present to other specialities. Another important difference was that neuro-Wilson disease contributed to nearly one-fifth cases of gray matter DBD in our study in contrast to the data from developed countries where it was rarely reported. The exact reason for this disparity is not clear. One plausible reason could be that our children presented early with neurological manifestations compared to the hepatic manifestations and hence were seen in the Pediatric Neurology clinics before the gastroenterology clinics.

In conclusion, our study highlights the burden and spectrum of gray matter DBD in children. The clinic-based prevalence of DBD and gray matter DBD is high. Gray matter DBD contributed to more than one-third of DBD in children, and the most common disorders are Wilson disease, NCL, and NBIA. Timely diagnosis is important for the prevention of recurrence in subsequent pregnancies. Our single-center study is limited by the cross-sectional nature, and prospective studies with long-term follow-up and underlying genetic confirmation of all patients may provide better understanding of inherited DBD and their phenotypic–genotypic correlation. Nevertheless, our study adds to the literature on the burden of inherited DBD in India and provides age-based etiological classification. This information can be helpful in clinical decision making and ordering of specific tests. With increasing availability of clinical expertise from pediatric neurologists and better diagnostic facilities including genetic studies in several centers across India, we can expect better diagnosis and characterization of DBD in near future. Population-based and multi-centric studies are warranted to identify the true burden of these rare disorders. The establishment of a DBD registry in India is highly desirable that would eventually pave way for more collaborative research and exploration of novel therapeutic options.

What this paper adds

- Clinic-based prevalence of DBD and inherited gray-matter DBD was 8.2% and 3.1%, respectively.
- Inherited gray-matter DBD constitute 37% of DBD cases.
- Majority of children present before 5 years of age.
- Most common inherited gray-matter DBD in children are Wilson disease, NCL, and NBIA overall.
- Most common gray-matter DBD are NBIA and Rett syndrome in children <2 years; NCL and AT in children aged 2–5 years, and Wilson disease and NCL in children aged 6–12 years.

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Conflicts of interest

There are no conflicts of interest.

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