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Reducing the burden of neurological disorders in children in India- Mission Possible!

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SUMMARY

The burden of neurological disorders in children in India is enormous. Unlike that in developed countries, largely preventable conditions such as epilepsy, CNS infections, and neurodevelopmental disorders constitute over 80% of the burden. According to UN estimates there are ≈ 40 million disabled children in India. An estimated 5 million children in India suffer from epilepsy. Neurocysticercosis accounts for >60% of acquired epilepsy, 20% of our neurology OPD cases, and for > 1500 children seen annually in our clinic. Neurological illnesses constitute about a fourth of pediatric emergencies, and over a third of PICU admissions. CNS infections are responsible for 60% of non-traumatic coma and > 60% of refractory status epilepticus in hospital and for serious sequelae in ≈ 40% children. Cerebral malaria and tubercular meningitis cause significant neuromorbidity in many regions. Preventable birth asphyxia occurs in 0.51 million newborns per year and is a risk factor in >50% cases of cerebral palsy. Preventable causes of acquired cerebral palsy continue to be seen over 2 decades in ≈ 20% cases; of these CNS infections and kernicterus account for >60% and >35% of cases. In India 71 million people have iodine deficiency; 5.8% cases of mental retardation in North India are because of inborn errors of metabolism; upto 70% of visual and 50% of hearing disabilities are preventable.

Proven preventive strategies against most of these conditions exist. Over 75% of' meningitis can be prevented through universal immunization. Hib meningitis is almost eliminated from UK and USA after universal Hib immunization; in our hospital the

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overall burden of meningitis decreased by about 50% and that of Hib meningitis from 32% to almost nil after introduction of immunization. Japanese encephalitis (JE) has also been eliminated from Japan, Korea and China after vaccination; we too can stop devastating outbreaks of JE and reduce the annual burden of 8247 cases with vaccination. Neurocysticercosis and JE can be fully controlled with improved sanitation, animal husbandry and public education; consequently the incidence of epilepsy can be reduced. Mass human chemotherapy with niclosamide and praziquantel can reduce intestinal tapeworm by 90-95%. Vaccination and chemotherapy of pigs can reduce cysts by 99.9%. Birth asphyxia can be reduced by almost 50% with community based interventions. Iodine supplementation program has improved cognitive and developmental scores of babies. Newborn screening for metabolic disorders can reduce neuromorbidity and save about 10,800 lives annually.

Secondary prevention is equally important. Immediate appropriate antibiotic therapy significantly reduces mortality and morbidity of bacterial meningitis. Early cysticidal therapy increases resolution of neurocysticercosis lesions and reduces seizures. Therapeutic hypothermia has a relative risk reduction of 25% on mortality and neurodevelopmental disability in asphyxiated infants. Kernicterus can be eliminated with simple interventions. Acute shortage of pediatric neurologists in India necessitates training of medical officers and pediatricians at all levels to ensure early appropriate management of common neurological disorders in children.

The burden of neurological disorders in children in India is enormous with overall prevalence rate of 1-3% in children <5 years of age (1). In a population-based study from North India, the prevalence of major neurological disorders among children <10 years of age was 0.7% (2). Unlike those in developed countries, largely preventable conditions such as epilepsy, central nervous system (CNS) infections, and neurodevelopmental disorders constitute over 80% of the burden in childhood in developing countries (3).

A. Childhood Epilepsy :

An estimated 5 million children in India suffer from epilepsy. The prevalence of epilepsy in India is estimated between 5.4-22.2 per 1000 population (4, 5). Each year we see approximately 30,000 patients in our pediatric neurology outpatient department (OPD); epilepsy constitutes 85% of these. In our house-to-house survey of 3684 children in the age group 1-18 years, the incidence of epilepsy was 6.24 per 1000 population (5.48 urban, 6.99 rural) for Chandigarh (6). The treatment gap in India varies from 38-78% (7, 8); our study showed a treatment gap of 22% in Chandigarh inspite of relatively good health-care facilities and predominantly educated population (6). Extrapolating this to the total number of children with epilepsy,

approximately 1.1 million children do not get proper treatment inspite of being diagnosed with epilepsy. There are several acquired and preventable causes of epilepsy in addition to genetic causes in India such as infections and neurodevelopmental disorders such as Cerebral Palsy (CP) (9).

a) Infectious Causes :

(i) Neurocysticercosis

Neurocysticercosis is the commonest cause of acquired epilepsy in our country (9). NCC constitutes almost 30% of epilepsy cases seen in our OPD and causes >60% of partial seizures in children (10). Over 1500 cases with NCC are seen in our clinic annually. In our series of 500 children with NCC (11), we found that >90% presented with seizures-mostly (83.7%) partial seizures. Most (76%) children had single enhancing lesions on computed tomography (CT) (Table 1) (11).

Preventive Strategies :

Primary

NCC can be prevented by ensuring proper hygiene and sanitation, community interventions and enforcing strict animal husbandry and meat inspection procedures (12). Mass human chemotherapy with niclosamide and praziquantel can reduce intestinal tapeworms by 90-95%. Vaccination with newer effective vaccines such as TSOL18 and treatment with oxfendazole of pigs has been shown to reduce cysts by 99.9% (13, 14). An educational program of farmers in Kenya increased their awareness about limiting exposure to tapeworm eggs and about tethering their pigs (15).

Secondary

There was considerable controversy regarding treatment of enhancing lesions due to NCC with cysticidal therapy as these lesions were thought to represent degenerating lesions. Our placebo controlled study on 63 children showed that the use of Albendazole therapy was associated with a significantly faster and increased resolution of single lesions at 1 month (41% vs. 16.2%) (p 0.05) and after 3 months (64.5% vs. 37.5%) ($p<0.05$). Seizure recurrence after 4 weeks was less in the Albendazole treated group (31.3%) versus placebo group (12.9%) (Figure1) (16).

Subsequently other studies confirmed these findings and a recent Cochrane analysis concluded that cysticidal therapy was effective in increasing the resolution of lesions and in decreasing seizure recurrence (17). Based on this evidence the American Academy of Neurology recently recommended the use of cysticidal therapy for the treatment of enhancing lesions (18). However, the treatment involved administration of cysticidal therapy for 4 weeks and anti-epileptic therapy for two years. Our

Table 1: Signs and symptoms at presentation and CT findings in 500 children with NCC

Sign or symptom	**Number of cases (%) (N=500)**
Seizures	474 (94.8%)
Nausea/vomiting	157 (31.4%)
Headache	141 (28.2%)
Papilledema	33 (6.6%)
Motor neurodeficits	20 (4%)
Cranial nerve palsy	6 (1.2%)
Extraneural cyst	3 (0.6%)
Lesion characteristic on CT	**Number of cases (%) (N=500)**
Single	380 (76%)
Multiple	120 (24%)
Ring-enhancing	410 (82%)
Disc	59 (11.8%)
Edema	287 (57.4%)
Calcification	75 (15%)

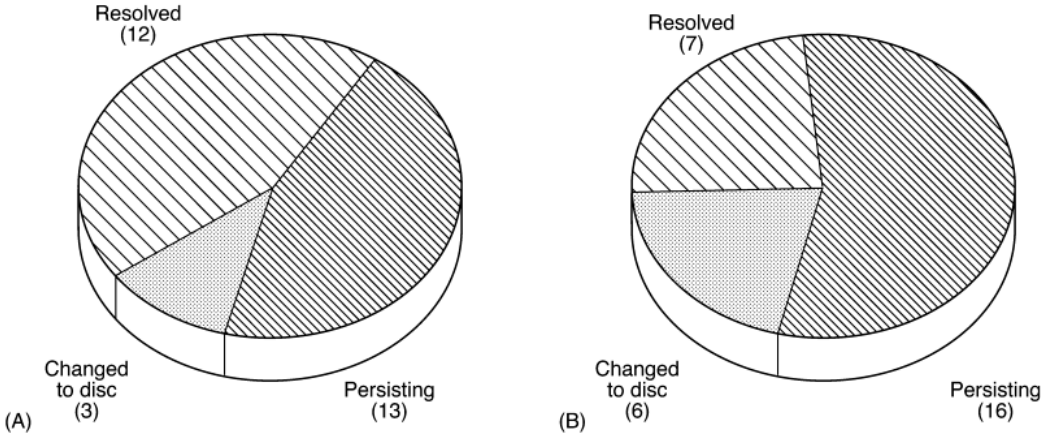

Figure 1: Comparison of single enhancing lesions on 1-month CT between (A) albendazole and (B) placebo

subsequent randomized study showed that 7-day therapy was as effective as 28-day therapy in children with single lesions (19). It is now our practice to use short-duration albendazole therapy in children with single lesions. Similarly in another randomized study, one year of antiepileptic therapy was found to be as effective as two years of antiepileptic therapy in children in whom the lesion had disappeared (20). Another study showed that the use of combination therapy with

praziquantel and albendazole may be better than either one alone (21), and that the use of steroids with albendazole is somewhat better than either alone (22). However larger trials are needed to establish these.

(ii) Other CNS Infections:

Acute symptomatic seizures occur in about one third of hospitalized cases of bacterial meningitis and late seizures (>72 hours) follow development of complications (23, 24). Meningitis is a common cause of febrile convulsive status epilepticus (25). Seizures are reported in 50-80% cases of Japanese encephalitis (26, 27), nearly 50% cases of tuberculous meningitis (28) and 22-50% cases of cerebral malaria (29). Prevention of these will be discussed later.

b) Neurodevelopmental Disorders and Disabilities :

Another important contributor to childhood epilepsy and intractable seizures is the presence of underlying developmental disorders and disabilities such as CP. In a study on 105 consecutive children (aged 1-14 years) with CP and active epilepsy and a retrospective cohort of 452 cases of CP, we found that 35.4% had epilepsy (30). The maximum incidence was seen in children with spastic hemiplegia (66%), followed by quadriplegia (42.6%) and diplegia (15.8%). Of the 105 children with active epilepsy, 38% had history of birth asphyxia. The mean age of onset of seizures was 18.9 months; 61% had seizure-onset in infancy. Generalized seizures were most common, followed by partial seizures, infantile spasms and myoclonic seizures. Social quotient values had a positive correlation with age of onset of seizures ($p<0.01$) and with better control of seizures ($p<0.01$) (30). Preventive strategies for these will be discussed later.

B CNS Infections :

a) Bacterial Meningitis :

Globally, 25,440 children <5 years of age were hospitalized with suspected meningitis in 2009 and from January-June 2010, 10,350 children <5 years of age with suspected meningitis were reported to the global Invasive Bacterial Disease-Vaccine Preventable Disease (VP-IBD) surveillance network; 51% from Africa and 21% from South East Asia (31). In children <5 years of age, the estimated incidence of H.Influenzae meningitis is 31 cases/1,00,00,00 (32), pneumococcal meningitis is 17 cases/100,00,00 (33), and that of meningococcal meningitis is 0.3-4 cases/100,000 populations in developed countries and 10-100/100,000 population in African counties (34). The prevalence of Hib meningitis was under-estimated in India as Hib is a fastidious organism to culture. In a PCR-based study, Hib could be detected in double the number of cases as were picked up on culture or latex-agglutination (35). In our hospital the incidence of Hib meningitis has remained

around 32-35% of the total meningitis cases. CNS infections were responsible for >60% cases of non-traumatic coma and constitute a huge burden in pediatric emergency and ICU (36); nearly 40% are left with serious sequelae (37, 38).

Preventive Strategies :

Primary

Over 75% of meningitis can be prevented through universal immunization. Vaccines against N. meningitidis, H. influenzae, and S. pneumoniae are currently available, but the protection afforded by each vaccine is specific to each bacterium and serogroups/serotypes. Routine use of polysaccharide-protein Hib conjugate vaccines has almost eliminated Hib meningitis/severe disease from developed countries. However in India, Hib meningitis still ranges from 1971-2433 cases/100,000 child-years of observation similar to western countries in pre-vaccination era (39).

Secondary

Immediate appropriate antibiotic therapy significantly reduces mortality and morbidity of bacterial meningitis. Use of shorter duration of ceftriaxone therapy (7 days versus 10 days) was equally effective in children over 3 months of age with uncomplicated meningitis (40). A recent large randomized double-blind study of 5 versus 10 days of ceftriaxone treatment conducted in six resource-poor

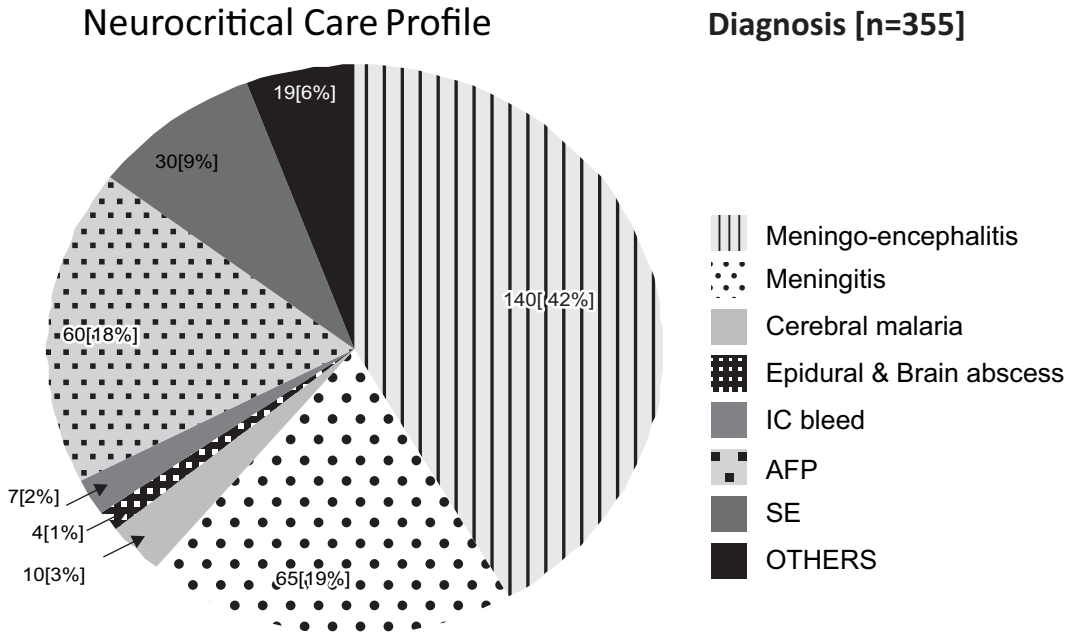

Figure 2: Neurocritical care profile of 355 children

countries found no significant difference in outcome of children (beyond the neonatal period) with uncomplicated bacterial meningitis due to Hib, pneumococci or meningococci, who were stable on day 5 of treatment (41).

In randomized controlled clinical trials, adjunctive therapy such as fluid restriction did not improve the outcome of acute meningitis in children (42). A Cochrane systematic review concluded that at least for settings with high mortality rates and where patients present late, evidence supports giving normal maintenance intravenous fluids rather than fluid restriction in the first 48 hours (43). CNS infections are responsible for >60% of refractory status-epilepticus (RSE) in hospital, which has a high mortality and morbidity. We found that intravenous diazepam infusion was effective in controlling seizures in RSE (44). However, due to the associated risk of hypotension and respiratory depression, diazepam infusion may be risky in places with no ventilators. Hence, we studied the efficacy and safety of intravenous sodium valproate and found it as effective as intravenous diazepam in controlling RSE, especially in resource limited settings (45).

Intra-cranial Pressure (ICP) monitoring for initial 24-48 hours can be helpful in maintaining adequate cerebral blood flow and perfusion in critically-ill children with CNS infections with a Glasgow Coma Scale (GCS) score ≤8 or abnormal CT findings. Cerebral perfusion pressure (CPP) targeted therapy, aimed at maintaining CPP>50 mmHg is useful for monitoring ICP; a CPP <40 mmHg is associated with high mortality (46).

b) Viral encephalitis :

Japanese encephalitis (JE) is the single largest cause of acute epidemic encephalitis worldwide and is responsible for 68000 cases/year and 13,000-20,000 deaths/year in Asia (47). Case fatality rate is 30% with severe neurological disabilities in survivors (48). It is transmitted by Culex mosquito, with water birds serving as natural reservoirs and pigs as amplifying hosts. In the 2005 epidemic in just five months, 5,737 cases and 1,344 deaths were reported from seven districts of Uttar Pradesh (49). Herpes simplex encephalitis is the commonest cause of sporadic encephalitis and has a high mortality and morbidity if treatment is delayed. Recently other viruses such as Enterovirus, Chandipura virus and Nipah virus are also being reported from various parts of India (50).

Preventive Strategies :

Primary

Preventive strategies are based on three pillars including national acute encephalitis syndrome surveillance, vector control and vaccination. The live attenuated vaccine has been shown to provide >90% protection. A cost-effectiveness analysis for 14 countries estimated that from 2007 to 2021, 193,676 cases, 43,446 deaths, 77,470 cases with sequelae, 6,622,932 disability-adjusted

life years (DALYs), and US$19 million in acute hospitalization costs could be avoided by immunization with the live, attenuated SA 14-14-2 JE vaccine through campaigns and implementation of routine immunization programs (51). Hence JE vaccination is a very cost-effective intervention. Although steps have been taken by the government to have active encephalitis surveillance and the Indian Academy of Pediatrics has also provided guidelines for this purpose (52), we are still lagging behind in immunization. In 2006, the Government of India initiated a five-year strategy (2006-2011) of JE vaccination campaigns to immunize children and adolescents between 1 and 15 years of age in high-risk districts, followed by introduction of JE vaccine into the routine immunization program. However, we have not yet achieved this. Increased production of JE vaccine and mass immunization particularly in hyperendemic areas is essential to prevent/ control JE epidemics.

Secondary

Early stabilization of cases, control of raised ICP and seizures can prevent the secondary morbidity associated with acute encephalitis. Prompt treatment with acyclovir can significantly reduce mortality and morbidity of herpes encephalitis.

c) CNS Tuberculosis :

CNS tuberculosis (TB) contributes considerably towards childhood neurological burden (53). In 2011 the estimated prevalence of tuberculosis was 125 cases per million globally with 0.5 million cases and 64000 deaths among children. India alone accounts for 26% of global cases of tuberculosis (54). About 10% of patients who have tuberculosis develop CNS tuberculosis, hence the number of estimated cases of tubercular meningitis is huge and children are most affected. Estimated mortality due to tubercular meningitis in India is 1.5 cases per 100,000 populations. HIV co-infection is associated with higher complications and case fatality rate (54). In a prospective study on 139 children with TBM, we found that two thirds were <5 years of age and three fourths presented late in stage 2 or 3 of the disease. About 30% children died; of the survivors, about half were left with serious neurological sequelae (unpublished data). In an analysis of 350 children with CNS TB, the mortality was 24.6% and 56.1% were left with neurological sequelae (unpublished data).

Preventive Strategies :

Primary

Prevention of CNS tuberculosis is a huge challenge (55). In a landmark development, the Ministry of Health and Family Welfare, Government of India, has taken important steps to establish the compulsory notification of tuberculosis in the country. A government order to this effect was issued on 7 May 2012. Childhood disease can be prevented by vaccination and by giving prophylactic isoniazid to children exposed to infectious

adults. Several tuberculosis vaccine trials are being explored to find the most effective vaccine (56).

Secondary

CNS tuberculosis requires at least one year of antitubercular therapy; hence ensuring drug availability and compliance particularly in the low socio-economic strata is a big problem, but can be achieved through the National TB Control Program. A recent Cochrane systematic review and meta analysis of 7 randomized controlled trials involving 1140 participants (with 411 deaths) concluded that corticosteroids reduced the risk of death or disabling residual neurological deficit in HIV-negative children and adults with tubercular meningitis (57).

C. Neuro-developmental disorders :

According to WHO estimates, worldwide 15-20% of children have disabilities; 85% of which are in developing countries (58). According to UN estimates 10% of the population has disability and of all persons living with disability, 35.9% are children and young adults; hence there are ≈40 million disabled children in India. The Census of India has determined that persons with disabilities (including visual, hearing, speech, locomotor, and mental disabilities) constitute 2% of the total population (59). This translates to almost 3 million children with disability.

The prevalence rate of mental retardation is about 20 per 1000 in general population, while that of developmental delays is about 30 per 1000 in children up to the age of 14 years (60). In an ICMR Task Force study, the prevalence of disability among children <6 years of age was found to be 8.8, 6.5 and 12.6/thousand in Delhi, Jaipur and Lucknow respectively (61). Nearly 70% of disabled children had a single disability while 30% had multiple disabilities.

In another community-based study in children <2 years of age, the overall prevalence of neurological disorders was estimated to be 28/1000 children. Prevalence of epilepsy was 1.3/1000, vision and hearing impairment each 0.6/1000, motor impairment 11/1000, and general developmental delay 26/1000 children in <2-years age-group. Perinatal, neonatal difficulties were the leading cause followed by congenital disorders and post-neonatal brain infection (62). The recent INCLEN study from 5 different geographical areas of India in children 2-9 years of age estimated that the prevalence of all NDD in 2-5 yrs of age is 11% and in 6-9 yrs old children is 15% (63). Dedicated house-to-house surveys in 3 villages using the WHO Ten Questions Screen in children aged 2-9 years in rural Chandigarh revealed a disability prevalence of 1.6% (64).

The spectrum of CP in our country is very different from that in the West, with a significant proportion (≃50%) being associated with birth asphyxia. In a centre based study on 1000 children with CP, spastic quadripledgia was the commonest

(63%) type of CP. Acquired preventable causes were seen in 22% cases (65). Kernicterus was responsible for 21.6% of acquired CP. In another study of 1212 children from the same centre it was found that though spastic quadriplegia still is the commonest type of CP (51%), however there is a relative increase in the proportion of spastic diplegia possibly because of increased survival of pre-term babies. CP due to CNS infections occurs in 57-64% cases and that due to bilirubin-encephalopathy occurs in 30% (66).

Inborn errors of metabolism :

The estimation of inborn errors of metabolism in India is 1 in 2497 newborns. An expanded newborn screening program of around 18,300 newborns from various government hospitals in Andhra Pradesh during 2000 revealed a high prevalence of inborn errors of metabolism - 1 in every 1000 newborns (67). Screening study of 1,12,269 newborn babies for amino-acid disorders reported that tyrosinemia, maple syrup urine disease, phenylketonuria, hyperglycinemia, homocystinuria and alkaptonuria were among the major aminoacidopathies (68).

Preventive Strategies :

Primary

Childhood Disability

A large proportion of childhood disability can be prevented by good antenatal, perinatal and neonatal care, avoidance of consanguineous marriages, ensuring safe delivery and timely immunization and neonatal screening for metabolic disorders. Birth asphyxia can be reduced by almost 50% with community based interventions involving training of health workers in neonatal resuscitation (69).

Secondary prevention is equally important. Therapeutic moderate hypothermia after perinatal asphyxia results in improved neurocognitive outcomes in childhood (70). Kernicterus can be entirely eliminated with simple interventions such as preventing Rh-isoimmunizations and promptly instituting phototherapy and exchange transfusion when needed.

There is an acute shortage of not only pediatric neurologists but even adult neurologists in India. As per WHO report, the number of neurologists in South East Asia is 0.07 per 100,000 population (71). There is an urgent necessity of training of medical officers and pediatricians at all levels to ensure early appropriate management of common neurological disorders in children.

Conclusion :

To conclude therefore, a huge burden of neurological disorders in childhood is secondary to preventable causes. Childhood epilepsy, CNS infections and childhood disability are inextricably interlinked. Simple preventive measures such as mass immunization, health care and sanitation

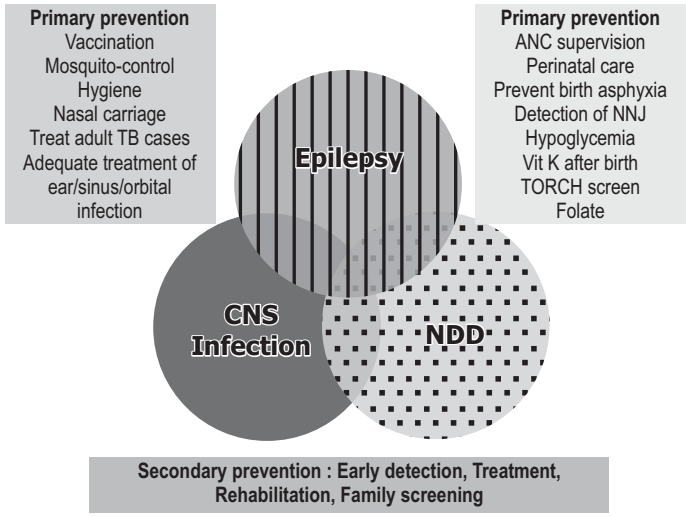

Figure 3: Proposed model for primary and secondary prevention of neurodisabilities in children due to CNS infections, epilepsy and Neurodevelopmental disorders (NDD)

can significantly reduce CNS infections and their associated epilepsy and disability. Antenatal care and safe institutional delivery can prevent almost half the case of cerebral palsy and mental retardation in our country and the associated epilepsy. Concerted efforts from the government, concerned professionals and the community can go a long way in reducing the burden of childhood neurological disorders (Figure 3).

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