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FULL-LENGTH ORIGINAL RESEARCH

Classifying etiology of infantile spasms syndrome in resource-limited settings: A study from the South Asian region

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Abstract

Objective: Etiological classification of infantile spasms syndrome (ISS) is important, considering the influence on prognosis based on the presence or absence of a known etiology. This study was performed to describe the limitations and difficulties experienced within the South Asian region when classifying the etiology of ISS according to the current recommendation.

Method: Data on healthcare indices and facilities related to management of ISS for the nine countries in the South Asian region were gathered by the South Asian West Syndrome Research Group. A Google survey was performed among three hundred and thirty pediatric neurologists in the region. The capacity within each country for investigating etiology of ISS according to current described benchmarks was evaluated. The difficulties experienced in this regard and the potential solutions were investigated.

Results: One hundred and sixty pediatric neurologists (response rate 48%) from Bangladesh (19/25), India (94/255), Myanmar (11/11), Nepal (6/8), Pakistan (19/25), and from Sri Lanka (7/8) responded. Three countries had no pediatric neurology services. Fifty-six percent attempted to classify ISS etiology according to classification outlined by International League Against Epilepsy in 2017. The facilities to perform metabolic, genetic, and immunological investigations were very limited. Lack of funding for investigations and poor laboratory support were the two most frequent barriers encountered. Sixty percent indicated that a separate classification is suitable for low-income setting; 78% suggested inclusion of separate category as "incompletely investigated" as an alternative solution to mitigate the barrier of achieving a better understanding of the etiological subtypes seen more frequently in this region.

Significance: The resources in South Asian region are limited to meet the recommendations for investigating etiology of ISS. Including the etiological

subcategory "incompletely investigated" is proposed as an alternative to understand the true proportions of children in this region, with a definite known etiology and those with an unknown etiology.

KEYWORDS
etiological classification, infantile spasms syndrome, South Asian region

1 | INTRODUCTION

Infantile spasms syndrome (ISS) is a developmental and epileptic encephalopathy (DEE) with a striking association with an underlying etiology in the majority. It may be related to abnormal brain structure and or abnormal function. The proportion with identifiable etiology, also referred to as "symptomatic," ranges from 60% to 80% depending on the country of origin of study and year of publication. A large-scale study from the National Consortium in Infantile Spasms in the United States reported that an underlying etiology is identifiable only in 64.4% of children even with detailed evaluation.[1] Those without a known cause are termed as unknown etiology or cryptogenic as in most previous publications. The benchmarks set in this study for the minimum investigations for each etiological category, suggested with reasonable precision, a two: one proportion between those with an identifiable etiology and those without. We will continue to refer to *etiology known* and *etiology unknown* to describe the categories symptomatic and cryptogenic etiologies, respectively.

Etiological classification of ISS is important, considering the prognosis variable on the presence or absence of a known etiology.[2,3] With advancement of technology, the understanding on etiologies underpinned with ISS has expanded. Thus, the etiological classification has grown from the basic symptomatic and cryptogenic types mentioned above to a much broader classification. The classification from the National Consortium in the United States had eight etiological subcategories.[1] Paciorkowski et al proposed a classification heavily weighted on genetic and biological subtypes.[4] These classifications expand our understanding of the different subtypes; however, the capacity for such detailed evaluation is limited to resourceful centers in few countries. Exhaustive classification does not influence the choice of initial treatment of ISS, except in those already known to have an etiology-specific ISS such as pyridoxine-dependent (*ALDH7A1*)-DEE, pyridox-(am)ine 5′-phosphate deficiency (*PNPO*)-DEE, and glucose transporter 1 deficiency syndrome (Glut1DS), treated with pyridoxine, pyridoxal phosphate, and ketogenic diet. In all other etiologies, the recommendation is for the use of steroids except for tuberous sclerosis (TSC) which is treated with vigabatrin.[5] TSC is essentially a diagnosis based on clinical and radiological features.

Key points

- The resources in the South Asian region are limited to meet the current recommendations for investigating etiology of ISS.
- Lack of funding for investigations and poor laboratory support are the two most frequent barriers impeding a complete etiological evaluation.
- Only about 50% of pediatric neurologists can attempt to classify etiology according to etiological subcategories in ILAE 2017 classification.
- Including the etiological subcategory *incompletely investigated* was considered an option to reduce the limitation posed by "Investigation Gap" when investigating ISS in the region.

The World Bank ranks countries based on the Gross National Income per capita. Presently, there are seventy-nine countries belonging to the lower two categories of low-income and low-middle income with more than 3.5 billion population.[6] These countries have severe limitations on government expenditure on healthcare services, many without free health care to all. Therefore, despite the relevance, applying these classifications to every child diagnosed with ISS is difficult in every setting. South Asia consists of nine countries, geographically located from the main continent to the Indian Ocean. It harbors 2 billion people, approximately 25% of the world's population. Except for Maldives (upper-middle income), all other countries fall to or below lower middle income countries.[7] Apart from the economy, social and cultural background of this region also contributes toward several neurological disorders seen in children. High rates of consanguinity, perinatal complications, and congenital and acquired central nervous system (CNS) infections are some of these factors, closely related to the etiopathogenesis of ISS. Although a higher incidence of ISS across northern latitudes was proposed in 2018,[8] the lack of research on epidemiology of ISS from South Asia in this meta-analysis

was glaring. The higher incidence reported in the Scandinavian countries could be an expression of research capacity and comprehensive record-keeping rather than a true increase of incidence in these countries. This cross-sectional survey was undertaken to describe factors that influence investigating etiology of ISS in the South Asian region and to describe what the pediatric neurologists in this region experience when establishing etiology.

2 | METHOD

This cross-sectional survey was conducted by the South Asian West Syndrome Research Group (SAWSRG), a collaborative group of pediatric neurologists (Bangladesh, India, Myanmar, Nepal, Pakistan, Sri Lanka) and pediatricians with special interest in neurology (Bhutan and Maldives) and an adult neurologist with interest in pediatric epilepsies (Afghanistan) from the South Asian region. SAWSRG was formed in early 2019 and subsequently expanded to include the nine listed countries. The sole purpose of the group is to improve the care of children with ISS through collaborative research.[9–11]

It was conducted from January to May 2021 and was granted ethical approval from the Ethics Review Committee of the Faculty of Medicine, University of Colombo (EC/21/45). Regional demographics and healthcare indexes related to childcare (a), availability of pediatric neurology services and facilities to classify etiology of ISS (b) were tabulated for each country by the study group members. The minimum requirements for classifying etiology were based on standards outlined for each etiological category by the National Consortium for Infantile spasms.[1] A literature survey was carried out to identify the etiologies and subtypes described within the South Asian region as of December 2020, which was resurveyed for new publications in June 2021 (c). Availability of consensus on management of ISS, government funding for investigating etiology, and public responsiveness toward investigations (d) were tabulated for each country by the study group members.

A Google survey was conducted among the pediatric neurologists, from the six countries in the region with established pediatric neurology services. The objective was to assess their practice regarding classifying etiology, the difficulties experienced during this process, and seek opinion regarding an achievable classification. A Delphi process, which elicited consensus among experts from different countries, was used to develop the questionnaire. The opinion of the experts which included judgment and agreement was obtained individually. JW acted as the moderator to accumulate these opinions. From an initial list of 24 questions, a final of 12 questions were selected based on consensus agreement by all 10 investigators. These questions had either one or multiple correct responses.

The pediatric neurologists were approached via email through professional groups by the respective members of the study group. Only those registered in respective professional bodies as pediatric neurologist or pediatrician with special training in neurology were contacted.

3 | RESULTS

The socioeconomical demographics and health indices pertaining to childcare in the region are shown in Table 1. These indices varied across the region, that is, attendance of all births by skilled healthcare workers seen in Maldives and Sri Lanka to highest neonatal and infantile mortality rates reported from Afghanistan and Pakistan. The government expenditure on healthcare ranged from 1.8% to 9.4% of the individual Gross Domestic Product.

Pediatric neurology services were available only in six countries. In Afghanistan and Bhutan, the services are provided by pediatricians or adult neurologists. Establishment of child neurology services in Maldives is still in its infancy. Availability of resources for performing electroencephalography (EEG) in children, neuroimaging, reference metabolic, and genetic laboratories in each country is listed in Table 2. Table 3 lists available literature in the region on ISS including described etiologies and Table S1 describes factors/measures that influence the evaluation of etiology.

Three hundred and thirty pediatric neurologists/pediatricians with special training in neurology were invited to participate. One hundred and sixty responded (response rate 48%). This included 19/25 (76%) from Bangladesh, 94/255 (36%) from India, 11/11 (100%) from Myanmar, 6/8 (75%) from Nepal, 19/25 (76%) from Pakistan, and 7/8 (87.5%) from Sri Lanka. The largest proportion (47%) were pediatricians who had completed a fellowship in pediatric neurology. There were 54 (34%) board-certified pediatric neurologists and the others were pediatricians with a special training or interest in child neurology (17.7%). A majority (36.3%) had experience of over 10 years in pediatric neurology. The others had service of 5-10 years (31%) and <5 years (32%). The average number of children newly diagnosed as ISS by each person for a year ranged from <10 in 16%, 10-20 in 29%, 20-50 in 32%, and >50 in 23%. A majority (47%) worked both in the government sector and in private healthcare facilities.

Almost all participants agreed on the importance of classifying the etiology of ISS; 71% indicated it as very important while 27% felt it was important. Fifty-six percent indicated that they investigate to achieve the etiological

TABLE 1 Summary of the demographic features and healthcare indices of the countries in the South Asian region

Demographical data	Afghanistan	Bangladesh	Bhutan	India	Maldives	Myanmar	Nepal	Pakistan	Sri Lanka
Birth rate Per 1000[31]	32	18	17	18	18	18	20	28	16
Size of birth cohort (million)[32]	1.08	3.04	0.01	25.6	0.06	0.9	0.6	5.4	0.3
GDP (Billion USD)[33]	19.29	30.25	2.53	2869	5.64	76	30.64	270	84
*Per capita Income (USD)[34]	507.1	1855.7	3316.2	2099.6	10 626.5	1407.8	1071.1	1284.7	3853.1
Government expenditure on health (% of government expenditure)[35]	1.8	2.98	7.61	3.39	9.41[b]	3.79	4.58	5.26	8.29
Availability of free health care	Yes	Yes	Yes	Yes[a]	Yes	Yes	Partial	Yes	Yes
Healthcare indices									
Neonatal mortality (per 1000 live births)[36]	35.9	19.1	16.6	21.7	4.9	22.4	19.8	41.2	4.3
Infant mortality (per 1000 live births)[37]	46.5	25.6	23.8	28.3	7.1[b]	35.76	25.8	55.7	6.1
Exclusive breastfeeding rates for 6 months (%)[38]	58	55	51.3	54.9	64	51.2	65	48	82
DTP3 immunization coverage (%)[32]	87	90	97	85	85[b]	91	91	72	99
Unattended home delivery percentage (%)[39]	49	47	4	19	0	40	42	31	0
Literacy rate (adult) (2016-18)[40]	43	73.9	66.6	74.4	97.7	75.6	67.9	59.1	91.7

[a]Limited to those below poverty line only.

[b]Ministry of Health (MOH) [Maldives] and ICF. 2018. Maldives Demographic and Health Survey 2016-17. Malé, Maldives, and Rockville, Maryland, USA: MOH and ICF.

TABLE 2 Estimates of human resources and infrastructure for care of children with neurological diseases including infantile spasms syndrome

Human resources and infrastructure	Afghanistan	Bangladesh	Bhutan	India	Maldives	Myanmar	Nepal	Pakistan	Sri Lanka
No of pediatricians	Unknown	1300	16	~35 000	26+65[a]	1000	509	4000	520
No of child neurologists	0	25	0	>250[a]	0	11	6	25	8
Availability of EEG in children's hospital (available number)	None	Yes (16)	Yes (1)	Yes (many)	Yes (2)	Yes (1)	Yes (5)	Yes (many)	Yes (7)
Radiological services									
No of CT machines	3	25	3	>1000	6	100	60-70	670	60
No of MRI machines	1	10	1	>300	4	25	15	25	20
No of Pediatric radiologists	0	Nil	0	~400[a]	0	3	Nil	5	1
Genetic services									
No of genetic laboratories	0	2	0	10-20	0	0	1	3	2
No of clinical geneticists	0	4	0	~100[a]	0	0	3	3	2
Metabolic services									
No of reputed metabolic laboratories	0	4	0	~10	0	0	5	2	Nil
Metabolic specialists	0	1	0	>70[a]	0	0	Nil	2	Nil
Average cost for single patient review, EEG and MRI brain (USD)	175	100	NA	40-50[b]	180	50	150	175-200	150

Note: NA—Not applicable as all services are free.

[a]Based on number of members in these respective Indian associations/societies (Indian Academy of Pediatrics, Association of Child Neurology, Indian Society of Pediatric Radiology, Indian Academy of Medical Genetics, and Indian Society of inborn errors of metabolism).

[b]Rough estimate.

TABLE 3 Literature on Infantile spasms syndrome and its etiology from the countries in the South Asian region

	Afghanistan	Bangladesh	Bhutan	India	Maldives	Myanmar	Nepal	Pakistan	Sri Lanka
No of articles on ISS indexed in PubMed or Scopus	None	5	0	>100	None	0	3	10	8
Abstracts if no full texts	None	NA	None	NA	None	2	NA	NA	NA
Reported incidence/ prevalence of WS per 1000	None	None	None	Age specific prevalence: 0.0628/1000	None	None	None		None
Proportion with**									
Structural etiology	None	None	None	82% (CI: 75%-89%)	None	None	None	75% (CI: 57%-89%)	68% (CI: 57%-78%)
Acquired structural insult	None	None	None	71% (CI: 61%-80%)	None	None	None	64% (CI: 55%-73%)	62% (51%-73%)
Described etiologies of WS	None	HIE/Perinatal asphyxia: 58% TORCH: 3.22% Brain malformation: 3.22%, Neonatal Hyperbilirubinemia: 3.22%, Neonatal sepsis: 3.2% Unknown: 6.5%*	None	Perinatal asphyxia/HIE (34.6%) Hypoglycemic brain injury (HBI) 16.7% Combined HIE and HBI (9%) Congenital brain malformations (3%) Other structural (10.7%) Infections (0.7%) Metabolic (0.7%) Proven genetic (7.2%) Not known/incompletely investigated (17.1%)^	None	• Perinatal asphyxia (27.7%) • Structural abnormality (15.7%) • CNS infection (8.4%) • Others (6%) • No known etiology (42.2%)#	• Perinatal asphyxia (50%) • CNS infection (22%)###	1. HIE 32% 2. CNS infection 13.6% 3. Congenital malformations- 13.6% 4. Perinatal stroke 5. 13.6% 6. Hypoglycemia 9% 7. IEM 9% 8. TSC 4.6%	Known- 71% Unknown −18% Incompletely investigated −11%
Average age of onset (months)	NR	5**	NR	NR	NR	5.5#	6###	4-6#	5**
Average lead time to diagnosis/ treatment (months)	NR	7.5**	NR	4.4**	NR	NR	NR	6	1.4**
Ratio of male in comparison to female	NR	2.1**	NR	2.6**	NR	1.44#	NR	NR	1.36**

Note: *[27], **[9], #[29], ##[26], ###[28], ^[41].

subcategorization outlined in the International League Against Epilepsy (ILAE) consensus report of 2017 at present. Twenty-five percent indicated that they could achieve only a simple classification as per the ILAE paper in 2010.[12] Only 18% indicated attempts to fulfill a more stringent etiological classification as proposed by Wirrell et al in 2015.[1] The availability of MRI imaging, metabolic, genetic, and immunological testing to them in all six countries is shown in Figure 1A; a comparison between India (more technically advanced) versus the other five countries is shown in 1B. The main barriers that prevent the neurologists from achieving a detailed etiological classification are shown in Figure 2. Lack of funding for investigations was the single most frequent obstacle. Projecting on how the investigation capacities would change over the next 5 years, a slightly higher percentage of 61% indicated confidence in reaching the ILAE etiological classification of 2017. Sixty percent of participants indicated that a separate classification is preferred for resource-limited settings. As a compromise to overcome this difficult situation, 78% of participants proposed the inclusion of a separate subcategory as *incompletely investigated* to the current classification.

4 | DISCUSSION

It is well established that *etiology unknown* or cryptogenic West syndrome is associated with better response to therapy, lesser number of relapses, better developmental outcome, and a possible mortality benefit.[13,14] Therefore, limitations for detailed investigation are an impediment to a clear understanding of the patient's prognosis. In fairness to the huge discrepancy of resources across the globe, it seems appropriate that a dialogue is generated on how etiology can be classified "adequately" by a pediatric neurologist anywhere in the world. In this study, we tried to illustrate the capacity of respective healthcare systems within South Asia and facilities available in each country to investigate etiology of ISS in par with the current recommendation. We found that the capacities were mostly below the requirement in general. Extreme variations were noted within the region. The study also reveals the difficulties experienced by child neurologists in the region in establishing etiology of ISS.

Infantile spasms syndrome literature predominates from the West, particularly North America and Europe. Data on incidence or prevalence of ISS from the East are limited. There is only a single study from India[15] to describe the prevalence of ISS from the South Asian region, despite one quarter of the world's population living within this geography. This results in a polarized understanding of etiologies particularly the proportions of *etiology known* and *etiology unknown* groups of ISS. The risks of pre-, peri-, and postnatal injury and infections being high due to greater consanguineous marriages, poor antenatal and natal care, and high rates of infections; the known etiologies could be expected to be higher in this region. The limited literature on ISS from this geographical setting is shown in Table 3, confirming this hypothesis. The average number of children with ISS newly diagnosed revealed in the survey also speaks of the disease burden in the region. The importance of understanding the etiologies more common to this region is to drive attention toward prevention of these risk factors. Strategies such as prepregnancy immunization for Rubella improved maternal nutrition and obstetric care, antenatal folic acid supplementation, vitamin K administration at birth, and improved vaccination coverage (BCG, HiB, and pneumococcal) for prevention of CNS infections are achievable objectives that would directly help to reduce the incidence of ISS. The higher proportion of *etiology known* group may also contribute to the lower response rates to therapy seen in this region,[16] requiring a greater vigil in treatment advocation. A similar situation of paucity of information on etiology due to investigative constraints as well as poor record-keeping is likely in the South American[17] and African continents.[18] ILAE has recognized these difficulties in the

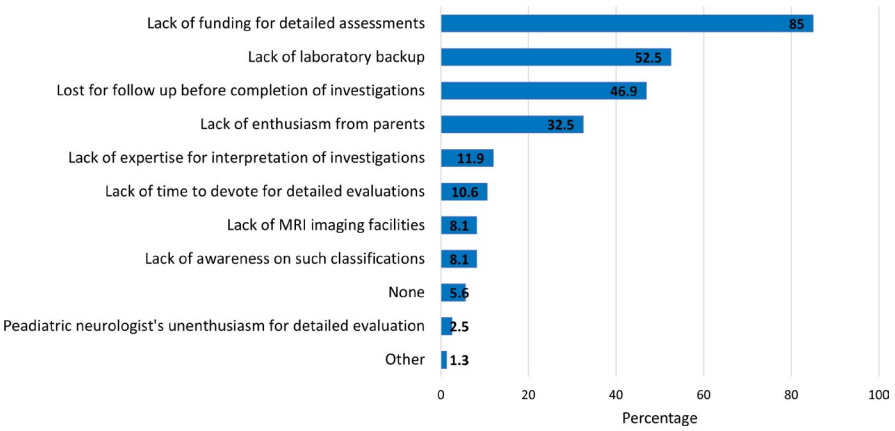

FIGURE 1 The availability of recommended investigations for establishing etiology according to ILAE etiological classification within the public and or private sector: A. in the hospitals of all participating pediatric neurologists and B. Distribution of these facilities across India and all other countries (n = 160)

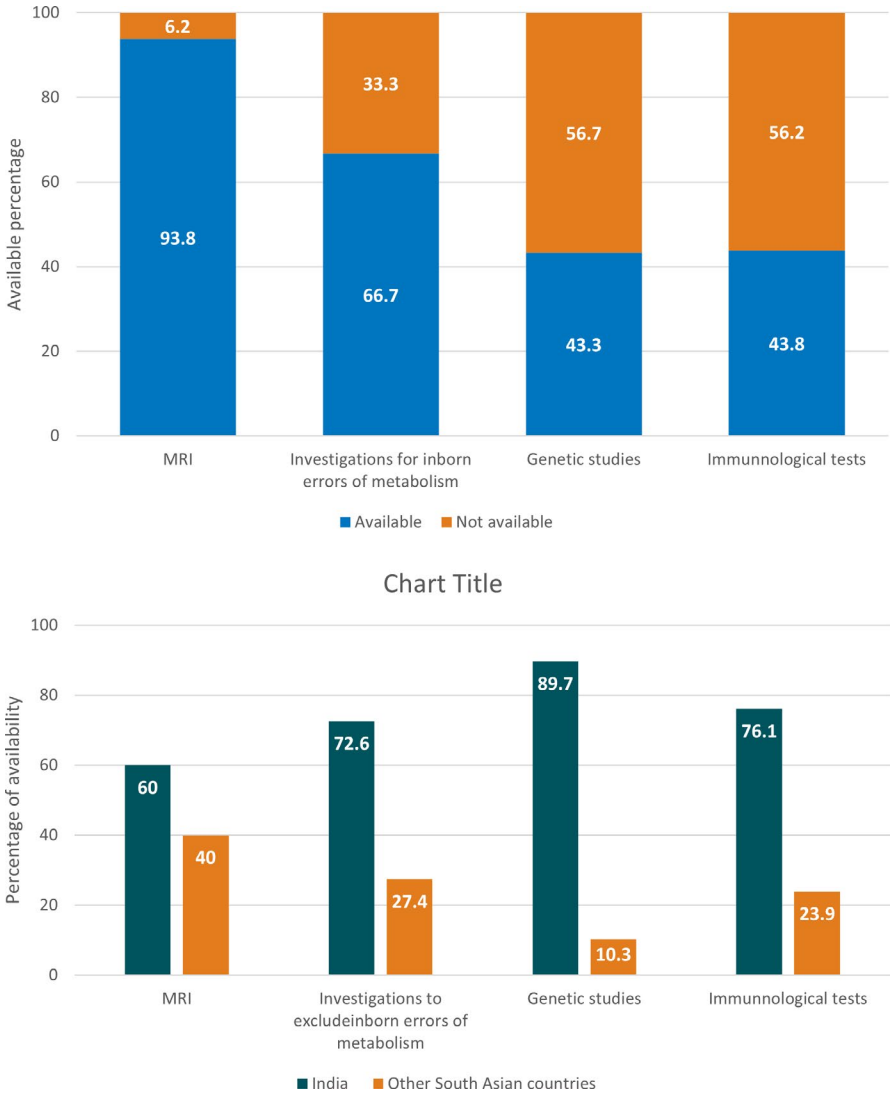

FIGURE 2 Difficulties and obstacles when investigating etiology of ISS by pediatric neurologists in South Asian countries (N = 160)

upcoming proposed classification and definition of epilepsy syndromes in the neonate and infant.[19]

The descriptions in yesteryears classified ISS etiology to three groups: symptomatic, cryptogenic, and idiopathic. Following the proposals from the ILAE in 2010, the classification was expanded to structural, genetic or metabolic, and unknown.[12] Though known etiology accounted for nearly 80% in earlier documentations, detailed evaluation by the National Infantile Spasms consortium, established that the proportion of children with symptomatic etiology was limited to 64.4%.[1] Interestingly, 85% of this group with known etiology had their etiology diagnosed with only a detailed clinical evaluation and neuroimaging. It is noticed that the 61% with identifiable etiology described in the UKISS trial[20] is rather close to the 55% reported by the US consortium. Unlike the US study, UKISS did not have an exhaustive strategy for investigation. The proximity of the percentages suggests that yield from extensive investigations will improve the proportion only by little. Since MRI was available in most settings evaluated in the current study, one could estimate that accurate diagnosis of etiology is achievable in 80%-85% of ISS in this region using clinical assessments and imaging.

Recent literature highlights the increasing numbers of genetic variations, mostly de novo, being associated with ISS. Extensive classification scheme based on the type of variation has also been proposed.[4] This genetic subgroup is very unlikely to be diagnosed much in the geography of the current paper, as well as many other low-resource settings. Epidemiologically, genetic and particularly metabolic[21] subcategories contribute to a small proportion of symptomatic ISS. In a recent study from India, genetic etiology was identified in 10% of children with ISS (39% of children with ISS and normal neuroimaging) even after detailed investigations,[22] while none had an identified metabolic etiology. Similarly, the proportions of ISS with immunogenic etiology is likely to be miniscule; there were none identified in the National Infantile Spasm Consortium.[1] On the other hand, even within the most exhaustive classifications, there are other etiologies

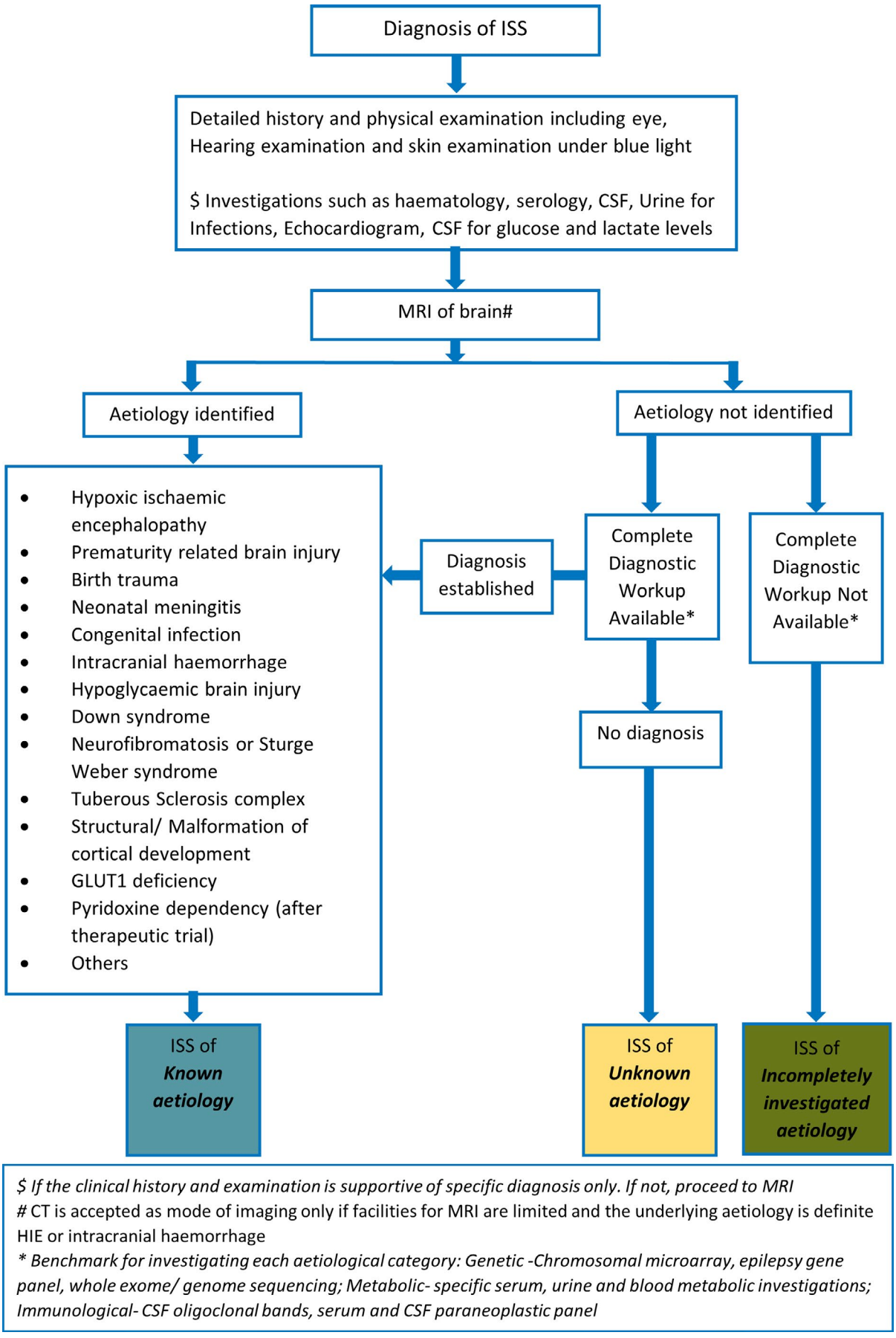

FIGURE 3 Algorithm for classifying etiology of infantile spams syndrome (ISS) in resource-limited settings

of ISS such vitamin B12 deficiency, described within the region,[23] being unrecognized. There may be other ambiguous situations such as separating infective etiology over structural cause in babies who develop ISS due to intrauterine Zika and cytomegalovirus infections.[24]

Contrary to figures from studies in the West, larger proportions with known etiology such as hypoxic ischemic encephalopathy (27%-58%)[9,25–27], and CNS infections (8%-22%)[28,29] are reported in this geographical region (Table 3). Neonatal hypoglycemia is an important etiological factor in India.[22,30] Therefore, using detailed history and MRI imaging, a significant proportion of children in our setting can be identified to have an etiology. The proportion due to genetic and metabolic subgroups which are difficult to diagnose may be small. Introduction of an etiological subcategory as *incompletely investigated*, as done in the UKISS etiological subclassification, where these rare categories can be included will help the clinicians to accomplish a reasonable understanding of the prevailing etiologies in resource-limited settings. This subdivision of the *incompletely investigated* category in the UKISS study accounted for only 6%. However, it facilitated a satisfactory understanding of the etiology in balance 94%. Majority of pediatric neurologists who participated in our study clearly favored inclusion of *incompletely investigated* as a separate subcategory in classifying etiology of ISS. It will improve the distinction of those definitely *without a known etiology* from those with no etiology due to incomplete evaluation. However, the *incompletely investigated* category will carry no weight for prognostication. We have proposed an algorithm that can be followed to achieve this subcategorization (Figure 3). This will facilitate distinction of the group with definite known etiology from the definite unknown group. This will enable a reliable comparison of etiologies across geographies.

One of the drawbacks in this study is that there is heterogeneity in the availability of services and expertise across countries investigated. This is directly influential in the availability and performance of investigative workup and the response to the survey. In this region, apart from resource limitations, other constraints contribute toward achieving a clear etiological classification. These include negative public attitude toward genetic etiologies, being lost for follow up and absence of systematic documentation of investigative findings. The survey did not explore different ways to mitigate the difficulty of investigation in the region, but only sorted opinion on usefulness of inclusion of subcategory as "incompletely investigated."

5 | CONCLUSION

This study describes the health-related demographics and resources available within the nine South Asian countries linked to the management of ISS. It also investigated the practical difficulties faced by the child neurologists in this setting for investigating children with ISS. The majority of study participants proposed the inclusion of the subcategory "incompletely investigated" into the etiological classification of ISS. In the discussion, it focused on the impact of resource limitation on achieving a satisfactory classification of etiology of ISS and postulated for others in similar resource-stricken countries. We envisage a dialogue on these observations of "investigation gap" in some parts of the world, so that a better understanding of the true proportions of etiologies of ISS across the globe will be facilitated.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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