

# SUBACUTE SCLEROSING PANENCEPHALITIS IN CHILDREN: RISK FACTORS, CLINICAL AND PARACLINICAL CHARACTERISTICS, DIFFERENTIAL DIAGNOSIS AND CENTRAL NERVOUS SYSTEM DRUG DELIVERY STRATEGIES

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## Abstract

Subacute sclerosing panencephalitis (SSPE) is a fatal, slowly progressive disorder of the central nervous system caused by persistence of a defective measles virus in neurons and glia. It has re-emerged wherever measles has returned, now affecting younger children after shorter latency and with a more fulminant course than in the historical literature. This review synthesises current evidence on risk factors, clinical and paraclinical characteristics, differential diagnosis and treatment of paediatric SSPE, with particular attention to the pharmacological problem that defines its therapeutics: the drug must reach an intracellular, cell-associated virus behind an intact blood–brain barrier. Age at measles infection is the dominant risk factor, post-measles risk rising from approximately 1 in 1367 for measles acquired before five years of age to 1 in 609 for measles acquired before twelve months. Diagnosis rests on the modified Dyken criteria, in which demonstration of intrathecally synthesised anti-measles IgG is decisive; the periodic Radermecker complex is highly specific but frequently absent early, and magnetic resonance imaging is a staging and exclusion tool rather than a diagnostic test, being normal in a substantial proportion of children at presentation. No disease-modifying therapy has established efficacy. Orally administered ribavirin fails because cerebrospinal fluid concentrations do not reach virustatic levels, which is why intraventricular delivery through an implanted reservoir has been the principal route investigated for both ribavirin and interferon-alpha. The single randomised controlled trial, of aprepitant, was negative for clinical outcomes. Timely two-dose measles vaccination remains the only intervention of demonstrated effectiveness, and a resource-stratified diagnostic pathway is proposed for settings lacking advanced immunology, video-electroencephalography and neurosurgical drug delivery.

**Keywords:** Subacute sclerosing panencephalitis, Measles virus, Blood–brain barrier, Intraventricular drug delivery, Interferon-alpha, Ribavirin, Electroencephalography, Differential diagnosis

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## Introduction

Subacute sclerosing panencephalitis (SSPE) is a progressive inflammatory and neurodegenerative disorder of the central nervous system that follows natural measles infection after a latency usually measured in years<sup>1,2</sup>. It is regarded as uniformly fatal and it is not vanishing: every setting that has

experienced a lapse in measles control has subsequently reported a cluster of cases<sup>3, 4</sup>. SSPE therefore occupies an unusual position in paediatric neurology — entirely preventable by a vaccine that has existed for six decades, yet, once established, untreatable by any agent of proven efficacy.

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Two features make SSPE pharmacologically instructive rather than merely rare. The pathogenic agent is not a replicating, budding virus in the circulation but a defective, cell-associated measles virus that spreads directly from neuron to neuron, largely shielded from humoral immunity<sup>5, 6</sup>. The target compartment is the brain parenchyma behind an intact blood–brain barrier. Any candidate therapy must therefore satisfy two conditions simultaneously: activity against a persistent, mutated virus, and delivery to the central nervous system at virustatic concentrations. The failure of oral ribavirin despite convincing *in vitro* activity is the clearest demonstration in the field that the second condition is not met automatically by the first<sup>7</sup>.

The clinical corollary is that diagnosis must be secure before invasive or expensive delivery strategies are contemplated, and that the diagnostic pathway in low- and middle-income settings must be built around what is actually available. Children present late — the great majority are already in clinical stage II or beyond when first investigated<sup>8, 9</sup> — so any intervention that improves outcome must act on the interval between first symptom and first investigation rather than on the sophistication of the investigations themselves.

This review summarises the risk factors identifiable from medical-history data; describes clinical, neurophysiological, neuroimaging and immunological characteristics with their reported denominators; sets out a structured differential diagnosis; and appraises therapeutic options with explicit attention to route of administration and central nervous system drug delivery. A resource-stratified pathway is proposed for children aged 0–18 years.

## Literature search strategy

PubMed/MEDLINE, Scopus, Google Scholar and regional Russian- and Uzbek-language sources were searched for records published between January 1979 and September 2026, combining the terms “subacute sclerosing panencephalitis”, “SSPE”, “measles virus”, “children”, “electroencephalography”, “magnetic resonance imaging”, “cerebrospinal fluid”, “interferon”, “ribavirin”, “isoprinosine”, “intraventricular” and “blood–brain barrier”. Population-based studies, cohorts, case–control studies, randomised trials and systematic reviews were prioritised; case reports were used only to illustrate atypical presentations or delivery-route experience. Country, study period and denominator are stated for every numerical claim. The 50 most relevant sources were retained.

## Epidemiology and the post-measles risk denominator

Most disagreement about SSPE incidence is in reality disagreement about denominators. Incidence expressed per million population, per million children and per 100 000 measles cases behave

differently, and only the last measures post-measles risk<sup>1</sup>. The widely cited global estimate is 4–11 SSPE cases per 100 000 measles cases, rising to approximately 18 per 100 000 when measles is acquired in the first year of life<sup>10, 11</sup>; expressed per population, worldwide incidence has ranged from 0.2 to 40 cases per million per year, with a reduction of 82–96% between 2000 and 2016 in countries that achieved higher coverage<sup>12</sup>.

Two modern studies show how much the denominator assumption matters. In Georgia, 16 cases diagnosed during 2008–2017 gave a crude risk of 1 per 1396 measles cases reported in the 2004–2005 outbreak (8377 cases); adjusting for 50%, 25% and 10% reporting completeness moved the estimate to 1:2792, 1:5584 and 1:13 960 — a tenfold range generated entirely by an assumption about surveillance quality<sup>4</sup>. In Germany, capture–recapture analysis of 31 children treated between 2003 and 2009 estimated a true total of 39 cases (95% CI 29.2–48.0) and a risk of 1:1700 to 1:3300 for children infected before five years of age, comparable to the risk of dying of acute measles<sup>13</sup>. Selected estimates with explicit denominators are given in Table 1.

**Table 1. Population-based and cohort estimates of SSPE occurrence and post-measles risk, with explicit denominators.**

| Country and period          | Population and denominator                                                                 | Principal finding                                                                                                              |
|-----------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| USA (California), 1998–2015 | 17 patients with SSPE; denominator = measles cases reported in the state                   | Risk 1:1367 after measles before 5 years; 1:609 after measles before 12 months; male:female 2.4:1 <sup>14</sup>                |
| Germany, 2003–2009          | 31 children from two independent sources; capture–recapture estimate 39 (95% CI 29.2–48.0) | Risk 1:1700 to 1:3300 after measles before 5 years, comparable to the risk of death from acute measles <sup>13</sup>           |
| Georgia, 2008–2017          | 16 SSPE cases; 8377 measles cases reported in the 2004–2005 outbreak                       | Crude risk 1:1396; 1:2792, 1:5584 and 1:13 960 at 50%, 25% and 10% reporting completeness. 11 of 12 (92%) with a known measles |

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| Country and period        | Population and denominator                                           | Principal finding                                                                                                                             |
|---------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                                                                      | history were infected at $\leq 2$ years <sup>4</sup>                                                                                          |
| United Kingdom, 2017–2019 | 6 children, all national referrals to the Virus Reference Department | Highest UK incidence since 2000; median age 5 years, median latency 3 years; all progressed to fulminant disease within 6 months <sup>3</sup> |
| Global, 2000–2016         | Multi-country coverage and surveillance data                         | 82–96% reduction in SSPE where measles vaccination coverage rose <sup>12</sup>                                                                |

A consistent pattern is visible across widely separated health systems: after a measles outbreak, SSPE reappears three to eight years later, in younger children, with shorter latency and a more fulminant course<sup>3,15</sup>. Every incident case is therefore a sentinel event, signalling with a lag of several years that a cohort of infants was left susceptible — a strong argument for linking SSPE notification to national measles surveillance.

The regional context illustrates the point. In Uzbekistan, WHO and UNICEF estimates place first-dose coverage at 96–99% in recent years, yet the Multiple Indicator Cluster Survey found that only 54.5% of children aged 12–23 months had received that dose before their first birthday<sup>16</sup>. Timeliness rather than eventual coverage determines how long an infant remains susceptible, and is therefore the variable most likely to predict future SSPE burden in such settings. Clinical descriptions of paediatric SSPE exist from the region<sup>17</sup>, but no population-based national incidence estimate could be identified.

#### **Risk factors identifiable from medical-history data**

A documented or probable history of wild-type measles is the necessary antecedent, and in the only substantial case-control study — 52 individuals from the US National Registry compared with matched playmate and hospital controls — cases were significantly more likely than controls to have had measles<sup>18</sup>. A documented history is nevertheless absent in a large fraction of contemporary series, including 46.67% of 30 children in Bangladesh<sup>9</sup> and 50% of 32 in India<sup>8</sup>, because measles in infancy is frequently subclinical, mild or simply not recalled. Absence of a measles history must therefore never

be used to exclude SSPE, and this should be stated explicitly in any local guideline.

Age at measles infection is the most consistently replicated risk factor and the effect is large. The same case-control study found age at measles among children who later developed SSPE to be significantly younger than among controls who had had measles<sup>18</sup>, and in Georgia 11 of 12 patients (92%) with a known measles history had been infected at two years or below<sup>4</sup>. The quantitative gradient in California ran from 1 in 1367 for measles before five years to 1 in 609 for measles before twelve months<sup>14</sup>. The explanation offered is immunological immaturity at infection, compounded by infants below vaccination age depending entirely on herd immunity and residual maternal antibody. The policy consequence is direct: infants are protected from SSPE not by vaccinating them earlier but by eliminating measles circulation around them<sup>15</sup>.

Vaccination requires careful statement, because this is where the literature is most often misread. The case-control study found that individuals with SSPE were less likely to have received measles vaccine than either control group, and found no difference in age at vaccination or in receipt of vaccine after natural measles; the authors concluded that the net impact of vaccination has been to prevent SSPE by preventing measles<sup>18</sup>. Vaccine strains have never been recovered from SSPE brain tissue, whereas wild-type virus has<sup>19, 1</sup>. Vaccination nevertheless does not confer absolute individual protection, and cohorts contain substantial proportions of vaccinated children — 91% of 32 in India<sup>8</sup> and 71.4% of 42 in Bangladesh<sup>20</sup>. Three non-exclusive explanations fit the molecular data: vaccine failure; subclinical wild measles acquired before the first dose; and receipt of the first dose after wild measles, a mechanism made explicit by the finding that 23 of 30 immunised Bangladeshi children were vaccinated after nine months of age<sup>20</sup>.

Incomplete and delayed immunisation recur throughout the literature. In the one cohort that tested the association formally (Pakistan,  $n = 47$ , 2020), unimmunised status was associated with earlier onset ( $P = 0.05$ ) and atypical presentation ( $P < 0.05$ ), and younger age at measles with earlier onset ( $P = 0.001$ )<sup>21</sup>; at national level a sustained upsurge in the same country was interpreted as a direct reflection of immunisation performance<sup>22</sup>. Reported risk factors, with denominators and evidence tier, are summarised in Table 2.

**Table 2. Risk factors for SSPE: reported associations, denominators and strength of evidence.**

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| Risk factor                      | Reported association and denominator                                                                                                                                                                                                         | Evidence tier                          |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Natural measles infection        | Necessary antecedent; cases significantly more likely than matched controls to have had measles (52 registry cases vs playmate and hospital controls) <sup>18</sup> . History absent in 46.67% of 30 <sup>9</sup> and 50% of 32 <sup>8</sup> | Case–control study; multiple cohorts   |
| Age at measles infection         | Risk 1:1367 if measles before 5 years vs 1:609 if before 12 months <sup>14</sup> ; 92% of Georgian patients infected at ≤2 years <sup>4</sup> ; risk approximately doubled if infected before 3 rather than 5 years <sup>13</sup>            | Strong and consistently replicated     |
| Absent or incomplete vaccination | Unimmunised status associated with earlier onset (P = 0.05) and atypical presentation (P < 0.05), n = 47 <sup>21</sup> ; national upsurge tracking immunisation performance <sup>22</sup>                                                    | Cohort with formal testing; ecological |
| Delayed first dose               | 23 of 30 immunised Bangladeshi children received measles vaccine after 9 months of age <sup>20</sup> ; only 54.5% of Uzbek children aged 12–23                                                                                               | Cohort; national survey                |

| Risk factor                               | Reported association and denominator                                                                                                                                                         | Evidence tier                              |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
|                                           | months received the first dose before their first birthday <sup>16</sup>                                                                                                                     |                                            |
| Community coverage gap                    | SSPE follows outbreaks with a 3–8 year lag; rising infant incidence is a collateral effect of under-vaccination in the surrounding community <sup>15, 3</sup>                                | Ecological, consistent across settings     |
| Male sex                                  | 79.9% of 144 in India <sup>23</sup> ; 87.5% of 32 <sup>8</sup> ; 88.1% of 42 in Bangladesh <sup>20</sup>                                                                                     | Near-universal; mechanism undetermined     |
| Rural residence, low socioeconomic status | 66.67% rural and 83.33% low socioeconomic status among 30 children <sup>9</sup> ; 85.3% low socioeconomic status among 34 <sup>24</sup>                                                      | Consistent but probably indirect           |
| Host immune and genetic susceptibility    | Candidate-gene associations in innate immune recognition and Th1 polarisation, including the IL-12/IFN-γ axis (51 case–control pairs) <sup>25</sup> ; reviewed comprehensively <sup>26</sup> | Hypothesis-generating; small, unreplicated |

Two cautions apply throughout: vaccination status obtained by parental recall rather than from a card or register is subject to substantial misclassification, and hospital-based series are biased toward severe, diagnostically certain cases. Studies quantifying risk should record the date and documented source of each dose, the age at each dose, and the timing of measles relative to the first dose, rather than a binary vaccinated/unvaccinated variable.

**Clinical presentation and staging**

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The Jabbour classification divides the illness into four stages: behavioural and cognitive change (I); myoclonic jerks, dyskinesia and ataxia (II); decerebrate or decorticate rigidity (III); and loss of cortical function with mutism (IV)<sup>27</sup>. A study of 118 patients from the Middle East refined this into six stages by adding a prodromal stage 0 and stages of improvement and relapse, and quantified the natural history: only 20% followed the classical sequence to death within one year, illness began in stage 0 in 32% and in stage 1 in 36%, and stage 0 lasted two years on average<sup>28</sup>. Stage-defining features and their paraclinical correlates are given in Table 3.

**Table 3. Clinical stages of SSPE with paraclinical correlates and management priorities.**

| Stage         | Clinical features                                                                                                                      | EEG and MRI correlates                                                                                                  | Management priority                                                                       |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| 0 (prodromal) | Subtle psychointellectual change; average duration 2 years <sup>28</sup>                                                               | EEG often normal or non-specific; MRI usually normal                                                                    | Recognition; avoid misattribution to school or family problems                            |
| I             | Deteriorating school performance, behavioural change, forgetfulness; in pre-school children, loss of acquired milestones <sup>20</sup> | EEG may be normal or atypical; MRI normal in a substantial proportion <sup>29</sup>                                     | Establish diagnosis; paired CSF and serum serology                                        |
| II            | Myoclonic jerks, dyskinesia, choreoathetosis, ataxia, seizures                                                                         | Periodic complexes typically time-locked to the jerk; subcortical and periventricular white-matter change <sup>30</sup> | Antiseizure and antimyoclonic therapy; nutrition and swallowing assessment; physiotherapy |

| Stage | Clinical features                                                       | EEG and MRI correlates                                                                             | Management priority                                                                     |
|-------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| III   | Decerebrate or decorticate rigidity, spasticity, progressive immobility | Complexes may become less regular; cerebral atrophy and diffuse callosal involvement <sup>30</sup> | Tone management, contracture prevention, aspiration precautions, palliative involvement |
| IV    | Akinetic mutism, autonomic instability, vegetative state                | Background attenuation; ventriculomegaly, diffuse atrophy, cystic encephalomalacia                 | Comfort-focused care; respiratory and feeding decisions agreed in advance               |

The clinically decisive observation is that children present late: the proportion already in stage II or beyond at diagnosis was 96.7% of 32 in India<sup>8</sup> and 96.7% of 30 in Bangladesh<sup>9</sup>, and 36.8% of 76 Turkish patients were already in stage III or IV<sup>29</sup>. Atypical presentations compound the delay, since visual loss, focal seizures, isolated behavioural change or a movement disorder may precede myoclonus by months<sup>31</sup>. In a series of 144 patients, outcome was determined more by stage at presentation than by any investigation result<sup>23</sup>.

## Neurophysiological and neuroimaging characteristics

The characteristic electroencephalographic finding is the periodic high-voltage slow-wave complex described by Radermecker: a stereotyped, bilaterally synchronous di- or triphasic slow wave of 100–1000  $\mu$ V at 1–3 Hz, recurring classically every 3–10 seconds and in stage II typically time-locked to a clinically visible myoclonic jerk<sup>11, 32</sup>. This temporal coupling is the single most specific neurophysiological observation available. Combined magnetoencephalography and electroencephalography in five children localised burst onset to the thalami and insula in 38–50% of analyses, with propagation to peri-central and frontal cortex, indicating a thalamocortical rather than purely cortical generator<sup>27</sup>.

A short recording may miss the complex entirely — one recurring every 15–20 seconds appears only

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three or four times per minute — so a minimum of 30 minutes reviewed in compressed epochs is required. In the largest single-centre series identified (77 patients aged 1–20 years, Pakistan), the record was normal in 14 (18.18%) and abnormal in 63 (81.81%), of which 53 (84.12%) showed periodic delta complexes and 10 (15.87%) atypical patterns<sup>33</sup>. Atypical patterns are commonest at onset, precisely when the diagnosis is most in doubt.

Two low-cost activation manoeuvres deserve emphasis. Among 26 children with suspected SSPE in Dhaka, only 8 (30.8%) showed typical periodic complexes before intervention, against 23 of 26 (88.5%) after intravenous diazepam or midazolam ( $P < 0.0001$ )<sup>34</sup>; sleep-deprived recording has separately been proposed where routine records are unrevealing<sup>35</sup>. The benzodiazepine study was small and lacked a non-SSPE comparison group, so its specificity is unquantified, but the pragmatic recommendation is clear: record awake and asleep, extend the recording, and consider an activated study before concluding that the electroencephalogram argues against the diagnosis. Magnetic resonance imaging is a staging and exclusion tool rather than a diagnostic test. In a retrospective cohort of 112 children with a mean age at onset of  $8.9 \pm 2.6$  years, abnormalities at presentation were subcortical white-matter change in 95 (84.8%), periventricular change in 76 (67.9%), splenial callosal involvement in 39 (34.8%), cerebral atrophy in 35 (31.3%) and brainstem involvement in 2 (1.8%); subcortical, periventricular, diffuse callosal and basal ganglia involvement were each significantly more frequent in stages III and IV ( $P < 0.05$ )<sup>30</sup>. Critically, no significant association was found between imaging findings and electroencephalographic abnormalities, or between imaging findings and cerebrospinal fluid measles antibody titres ( $P > 0.05$  for all)<sup>30</sup>. The three paraclinical modalities are therefore neither interchangeable nor redundant: each correlates with clinical stage but not with the others, so a normal result in one carries no information about the others. A normal first scan is common and is not evidence against the diagnosis: in a Turkish series the initial study was normal in 21 of 76 patients, 19 of them in stages I or II<sup>29</sup>. When imaging is normal in a child with a compatible syndrome, the correct action is to complete the serology and repeat imaging in 6–12 months. Because imaging is more often normal early, its availability constrains early diagnosis less than access to electroencephalography and serology — a conclusion with direct implications for resource allocation. Atypical patterns include bilateral putaminal and callosal change mimicking a metabolic disorder<sup>36</sup> and asymmetrical patchy lesions resembling acute disseminated encephalomyelitis<sup>37</sup>. Paraclinical findings are summarised in Table 4.

**Table 4. Paraclinical findings in paediatric SSPE: reported frequency, interpretation and feasibility.**

| Investigation                | Reported finding and denominator                                                                                                 | Interpretation                                                                                      | Feasibility in a district hospital         |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------|
| Routine EEG                  | Abnormal in 63 of 77 (81.81%); periodic delta complexes in 53 of 63 abnormal records (84.12%) <sup>33</sup>                      | Periodic complex time-locked to myoclonus is highly specific; a normal record does not exclude SSPE | High; requires $\geq 30$ -minute recording |
| Benzodiazepine-activated EEG | Typical complexes in 8 of 26 (30.8%) before and 23 of 26 (88.5%) after intravenous benzodiazepine ( $P < 0.0001$ ) <sup>34</sup> | Converts a non-diagnostic record in a child with a compatible syndrome; specificity unquantified    | High and inexpensive                       |
| Sleep-deprived EEG           | Proposed as an early diagnostic tool where routine records are unrevealing <sup>35</sup>                                         | Adjunct when the routine study is non-diagnostic                                                    | High                                       |
| MEG—EEG source localisation  | Burst onset localised to thalami or insula in 38–50% of                                                                          | Supports a thalamocortical generator; research tool                                                 | Very low                                   |

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| Investigation      | Reported finding and denominator                                                                                                                       | Interpretation                                                 | Feasibility in a district hospital |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------|
|                    | analyses, n = 5 <sup>27</sup>                                                                                                                          |                                                                |                                    |
| Brain MRI          | Subcortical white-matter change in 95 of 112 (84.8%); cerebral atrophy in 35 (31.3%); no correlation with EEG or CSF antibody (P > 0.05) <sup>30</sup> | Stages disease and excludes alternatives; not diagnostic       | Moderate                           |
| Initial MRI normal | Normal in 21 of 76 patients, 19 in stages I–II <sup>29</sup>                                                                                           | A normal early scan never excludes SSPE; repeat in 6–12 months | Moderate                           |

**Cerebrospinal fluid, serological and immunological changes**

Routine cerebrospinal fluid parameters are characteristically normal or near-normal, which is itself informative because it separates SSPE from acute encephalitis, in which pleocytosis and raised protein are expected; the one abnormal routine parameter is the globulin fraction, raised above 20% of total protein<sup>11</sup>. Demonstration of anti-measles IgG in cerebrospinal fluid is the decisive investigation. The classical thresholds embedded in the modified Dyken criteria — cerebrospinal fluid titre  $\geq 1:4$  or serum titre  $\geq 1:256$  — derive from complement-fixation and haemagglutination-inhibition assays and do not transfer to enzyme immunoassays reporting in international units per millilitre, a common source of laboratory confusion<sup>38</sup>. Addressing this, a Japanese group compared paired samples from three patients with SSPE (59 paired samples), 37 patients without SSPE and 2618 samples of unknown background: 56 of 59 SSPE samples (94.9%) showed cerebrospinal fluid

measles IgG  $\geq 0.5$  IU/mL together with a cerebrospinal fluid/serum ratio  $\geq 0.05$ , whereas non-SSPE cases showed values below 0.1 IU/mL and a ratio below 0.03, and only 20 background samples (0.8%) met the SSPE criteria<sup>39</sup>. The small number of patients means these are a framework requiring local re-derivation rather than universal cut-offs, but the principle of pairing an absolute concentration with a ratio is sound and directly implementable.

A raised antibody concentration may reflect genuine intrathecal synthesis or passive transfer across a damaged blood–cerebrospinal fluid barrier, and only the former is meaningful. The antibody index — the cerebrospinal fluid/serum measles IgG ratio divided by the albumin quotient — corrects for this; where albumin cannot be measured in both compartments the simple ratio should be used and its vulnerability to barrier disruption stated in the report. Oligoclonal bands are characteristically present and, unlike the transient banding of acute infection, may persist for life<sup>40</sup>.

Immunological studies consistently describe an incompetent rather than absent response: cytokine and lymphocyte-subset analyses show a response that fails to eliminate the virus despite high antibody titres<sup>41</sup>, and case–control work implicates the IL-12/IFN- $\gamma$  axis in susceptibility<sup>25</sup>. This is directly relevant to therapeutics, providing the rationale for immunomodulation with interferon rather than immunosuppression, which has no supporting evidence and a plausible mechanism of harm. Thresholds and their interpretation are set out in Table 5.

**Table 5. Cerebrospinal fluid and serological investigations in SSPE: thresholds, interpretation and limitations.**

| Investigation                            | Threshold or expected result         | Interpretation and limitation                                                                                          |
|------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Routine CSF cell count, protein, glucose | Normal or near-normal                | Normality supports SSPE and argues against acute encephalitis; pleocytosis should prompt reconsideration <sup>11</sup> |
| CSF globulin fraction                    | >20% of total CSF protein            | Minor criterion in the modified Dyken framework                                                                        |
| Anti-measles antibody (classical titres) | CSF $\geq 1:4$ or serum $\geq 1:256$ | Derived from complement fixation and haemagglutination inhibition; does not transfer to                                |

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| Investigation                      | Threshold or expected result                                         | Interpretation and limitation                                                                                                                           |
|------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                                                                      | enzyme immunoassay <sup>38</sup>                                                                                                                        |
| Paired CSF/serum measles IgG (EIA) | CSF $\geq 0.5$ IU/mL and CSF/serum ratio $\geq 0.05$                 | Present in 56 of 59 paired SSPE samples (94.9%); only 0.8% of 2618 background samples met the criteria. Assay-specific; re-derive locally <sup>39</sup> |
| Antibody index                     | CSF/serum measles IgG $\div$ albumin quotient, above local threshold | Corrects for blood-CSF barrier integrity; preferred where CSF and serum albumin can both be measured                                                    |
| Oligoclonal bands                  | Present and persistent                                               | Supports chronic intrathecal synthesis but is not specific; report band type <sup>40</sup>                                                              |
| CSF measles RT-PCR                 | Frequently negative                                                  | Low sensitivity; a negative result never excludes SSPE. Principal value is genotyping for surveillance <sup>19</sup>                                    |

**Diagnostic criteria and differential diagnosis**

The modified Dyken criteria comprise two major criteria — a characteristic clinical course and raised anti-measles antibody in cerebrospinal fluid — and four minor criteria covering the periodic electroencephalographic complex, raised cerebrospinal fluid globulin, characteristic brain biopsy findings and molecular detection of measles virus; two major plus one minor criterion are required<sup>38, 2</sup>. In practice the serological criterion carries the diagnostic weight, and the practical hierarchy in a resource-limited setting is unambiguous: paired serology is indispensable, electroencephalography is valuable and inexpensive, and imaging is desirable but dispensable.

In an endemic region SSPE must be excluded in any child with subacute or chronic progressive neuromotor impairment and regression, and it is probably the commonest cause of progressive

myoclonic epilepsy in low- and middle-income countries<sup>11</sup>. Table 6 compares the conditions that most often displace it. The most consequential error is to treat a child from a measles-endemic area empirically as autoimmune encephalitis without excluding SSPE, since immunosuppression has no evidence of benefit and a plausible mechanism of harm; the reverse error is equally damaging but less common<sup>37</sup>.

**Table 6. Structured differential diagnosis of paediatric SSPE.**

| Condition                            | Tempo and clinical signs                                               | EEG and MRI                                                                                                     | CSF and specific testing                                           | Key discriminator                                                       |
|--------------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------------------|
| Subacute sclerosing panencephalitis  | Weeks to months; cognitive regression then myoclonus, rigidity, mutism | Periodic complexes time-locked to myoclonus; subcortical and periventricular white-matter change, later atrophy | Normal routine profile; intrathecal anti-measles IgG <sup>39</sup> | Intrathecally synthesised measles IgG with a normal routine CSF profile |
| Acute disseminated encephalomyelitis | Days; monophasic, often post-infectious, encephalopathy mandatory      | Diffuse slowing; large asymmetrical patchy demyelinating lesions                                                | Mild pleocytosis; MOG antibody may be positive                     | Monophasic course and steroid response; SSPE can mimic it <sup>37</sup> |
| Autoimmune encephalitis              | Days to weeks; psychiatric features,                                   | Extreme delta brush in NMDAR disease; often                                                                     | Neuronal surface antibodies;                                       | Antibody positivity and immunotherapy                                   |

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| Condi-<br>tion                                            | Tempo<br>and<br>clinical<br>signs                                                           | EEG<br>and<br>MRI                                                                                      | CSF<br>and<br>speci-<br>fic<br>testin-<br>g            | Key<br>discrimina-<br>tor                                                                          |
|-----------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------|
|                                                           | seizures,<br>movement<br>disorder                                                           | normal<br>or<br>limbic<br>change                                                                       | pleocytosis<br>common                                  | response                                                                                           |
| Acute<br>viral<br>encephalitis                            | Hours<br>to<br>days;<br>fever,<br>altered<br>consciousness                                  | Focal<br>slowing<br>or<br>epileptiform<br>discharges;<br>temporal<br>change<br>in<br>herpes<br>simplex | Pleocytosis,<br>raised<br>protein,<br>positive<br>PCR  | Febrile<br>acute<br>onset<br>with<br>an<br>inflammatory<br>CSF                                     |
| Neurometabolic<br>disease<br>and<br>leukodystrophy        | Months<br>to<br>years;<br>regression,<br>spasticity,<br>no<br>myoclonus<br>time-<br>locking | Slowing;<br>symmetrical<br>confluent<br>white-matter<br>change                                         | Normal<br>measles<br>serology;<br>metabolic<br>screen  | Symmetrical<br>leukodystrophic<br>pattern<br>with<br>negative<br>measles<br>serology <sup>36</sup> |
| Progressive<br>myoclonic<br>epilepsy<br>of other<br>cause | Months<br>to<br>years;<br>myoclonus,<br>ataxia,<br>seizures                                 | Generalised<br>spike-wave,<br>photosensitivity;<br>atrophy                                             | Negative<br>measles<br>serology;<br>genetic<br>testing | Negative<br>intrathecal<br>measles<br>response                                                     |
| Primary<br>psychiatric<br>disorder                        | Weeks;<br>behavioral<br>change                                                              | Normal<br>EEG;<br>normal<br>MRI                                                                        | Normal                                                 | Absence of<br>any<br>neurology                                                                     |

| Condi-<br>tion | Tempo<br>and<br>clinical<br>signs       | EEG<br>and<br>MRI | CSF<br>and<br>speci-<br>fic<br>testin-<br>g | Key<br>discrimina-<br>tor                                          |
|----------------|-----------------------------------------|-------------------|---------------------------------------------|--------------------------------------------------------------------|
|                | ,<br>declining<br>school<br>performance |                   |                                             | gical<br>sign or<br>paraclinical<br>abnormality<br>on<br>follow-up |

**Therapeutics and the problem of drug delivery to the central nervous system**

No therapy has established efficacy in SSPE, and the evidence base is dominated by uncontrolled series confounded by a phenomenon that makes such data nearly uninterpretable: spontaneous remission or long-term stabilisation occurs in approximately 5–6% of patients without any treatment<sup>2, 42</sup>. Any single report of improvement after a novel agent must be read against that background rate. There is one randomised controlled trial: 62 patients received aprepitant 250 mg daily for 15 days in two courses two months apart (n = 31) or placebo (n = 31); the drug was well tolerated, but clinical status at six and twelve months did not differ and the only significant finding was a modest improvement in electroencephalographic score at twelve months (P = 0.015)<sup>43</sup>. The essentially negative result should be stated plainly.

The pharmacological obstacle is specific and well characterised. The measles virus in SSPE is cell-associated and spreads trans-synaptically within the brain parenchyma, so a systemically administered agent must cross the blood–brain barrier and achieve virustatic concentrations in tissue rather than merely in plasma<sup>5, 44</sup>. Interferon penetrates the blood–brain barrier poorly, which is the stated reason that the intraventricular route into the cerebrospinal fluid circulation has been preferred for it<sup>45</sup>. Ribavirin provides the clearest demonstration of the principle. It inhibits SSPE virus strains in vitro and in animal models, but oral administration produced no effect in patients because cerebrospinal fluid concentrations did not reach the levels that were effective in vitro; in hamsters, daily intracerebral administration improved survival in a dose-dependent manner and raised brain concentrations into the effective range, and the minimum inhibitory concentration against SSPE virus in brain was estimated at 5–10 µg/mL with complete inhibition at 50–100 µg/mL<sup>7</sup>. The therapeutic problem in SSPE is therefore not principally one of finding an active molecule but of delivering a known-active molecule to the compartment where the virus resides.

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Three delivery strategies have consequently been explored. Systemic oral administration is used for inosine pranobex (isoprinosine) at 50–100 mg/kg/day to a maximum of 3 g/day in three to five divided doses, which is feasible anywhere but of unproven benefit and, in published cohorts, frequently discontinued by families because of cost<sup>46, 42</sup>. Intraventricular or intrathecal administration of interferon-alpha or interferon-beta, typically one to three million units one to three times weekly, delivers the agent directly into the cerebrospinal fluid circulation and bypasses the barrier entirely, at the price of requiring an implanted reservoir, neurosurgical support and repeated aseptic access<sup>7</sup>. Combination of intraventricular interferon-alpha with oral inosine pranobex has been reported to induce remission or stabilisation in 44–55% of cases in uncontrolled series<sup>46</sup>. Continuous intraventricular infusion by subcutaneous pump has been described as a means of maintaining target ribavirin concentrations in cerebrospinal fluid without severe adverse effects<sup>7</sup>. The longest documented experience of the intraventricular route is a patient treated with  $1 \times 10^6$  units of interferon-alpha twice weekly through an Ommaya reservoir for 13 years, with oral inosiplex for the first five, who remained neurologically stabilised and sustained only one episode of bacterial meningitis over that period<sup>47</sup>. The adverse-effect profile of the intraventricular route is inseparable from the delivery method rather than the molecule: bacterial and chemical meningitis, interferon-induced encephalopathy and motor neuron toxicity are all reported with long-term repeated administration<sup>7</sup>. This shifts the risk–benefit calculation decisively where neurosurgical support is absent, and explains why the same regimen may be defensible in a tertiary centre and indefensible in a district hospital. In a 144-patient Indian cohort in which the majority received interferon, mortality nevertheless remained high<sup>23</sup>, and a critical appraisal from the same region concluded that invasive routes, cost and drug availability — not any absence of candidate agents — are the binding constraints in resource-constrained settings<sup>42</sup>. Therapies and routes are appraised in Table 7.

**Table 7. Appraisal of therapies used in SSPE by route of administration, evidence and feasibility.**

| Intervention and route              | Regimen reported      | Best available evidence and effect | Feasibility in a low-resource setting |
|-------------------------------------|-----------------------|------------------------------------|---------------------------------------|
| Measles vaccination (intramuscular) | Two doses of measles- | Consistent inverse relations       | High; uses existing immunisation      |

| Intervention and route                                      | Regimen reported                                                      | Best available evidence and effect                                                                                                                     | Feasibility in a low-resource setting                                  |
|-------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Interferon-alpha or -beta (intraventricular or intrathecal) | 1–3 million units, 1–3 times weekly <sup>7</sup>                      | Remission or stabilisation in 44–55% with oral inosine pranobex in uncontrolled series <sup>46</sup> ; one patient stabilised over 13 years via Ommaya | Very low; requires reservoir, neurosurgery and aseptic repeated access |
| Inosine pranobex / isoprinosine (oral)                      | 50–100 mg/kg/day, maximum 3 g/day, in 3–5 divided doses <sup>46</sup> | Benefit reported in about one third of cases in uncontrolled series; component of most combination regimens <sup>46, 42</sup>                          | Low; limited by cost and availability                                  |
| Measles vaccination (preventive)                            | Containment of vaccine                                                | High with SSPE incidence; 82–96% reduction where coverage rose 2000–2016 <sup>12</sup>                                                                 | High; infrastructure                                                   |

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| Intervention and route                                           | Regimen reported                                                                                                    | Best available evidence and effect                                                                                            | Feasibility in a low-resource setting                             |
|------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
|                                                                  |                                                                                                                     | a reservoir <sup>47</sup>                                                                                                     |                                                                   |
| Ribavirin (oral)                                                 | Systemic dosing                                                                                                     | No effect; CSF concentrations fail to reach in vitro effective levels <sup>7</sup>                                            | Not recommended on pharmacokinetic grounds                        |
| Ribavirin (intraventricular, including continuous pump infusion) | Titration to CSF concentration; target 5–10 µg/mL minimum inhibitory, 50–100 µg/mL complete inhibition <sup>7</sup> | Uncontrolled Japanese clinical development program; effect on clinical course reported, efficacy not established <sup>7</sup> | Very low; requires reservoir or implanted pump and CSF drug assay |
| Aprepitant (oral)                                                | 250 mg/day for 15 days, two courses two months apart                                                                | One randomised, double-blind, placebo-controlled trial (n = 62): no clinical difference at 6 or 12 months; EEG score          | Low; not recommended outside research                             |

| Intervention and route                          | Regimen reported                                  | Best available evidence and effect                                                                                                                     | Feasibility in a low-resource setting                                           |
|-------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
|                                                 |                                                   | improved (P = 0.015) <sup>43</sup>                                                                                                                     |                                                                                 |
| Corticosteroids and immunosuppression           | —                                                 | No supporting evidence; theoretical harm given an already incompetent antiviral response <sup>41</sup>                                                 | Available but inappropriate; exclude SSPE before empirical autoimmune treatment |
| Ketogenic or low glycaemic index diet (enteral) | Ketogenic ratio titrated to urinary ketones       | Uncontrolled experience including a low- and middle-income-country series; interpretation limited by the 5–6% spontaneous remission rate <sup>48</sup> | Moderate; requires dietetic support                                             |
| Antiseizure and antimyoclonic therapy (oral)    | Carbamazepine, levetiracetam, valproate, clobazam | Consistent clinical experience; carbamazepine has specific                                                                                             | High; established symptomatic care                                              |

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| Intervention and route | Regimen reported | Best available evidence and effect          | Feasibility in a low-resource setting |
|------------------------|------------------|---------------------------------------------|---------------------------------------|
|                        | clonazepam       | support for myoclonus in SSPE <sup>49</sup> |                                       |

The distinction to be drawn for families is between established and investigational care. Antiepileptic medication, nutritional and swallowing support, physiotherapy, respiratory care and palliative care are established, will make the child more comfortable and may extend life; in the Turkish registry 60 of 340 patients (17%) had died at two years, far below the 95% fatality quoted in older literature, an improvement attributed jointly to immunomodulators, supportive care and nutrition<sup>50</sup>. Isoprinosine, interferon, ribavirin and dietary therapy are investigational: they may help, have not been shown to help, are expensive, and in the case of intraventricular delivery carry procedural risk.

**A resource-stratified diagnostic and management pathway**

The pathway in Table 8 is organised so that every step except one is executable in a district hospital, and only the enhanced-resource step requires tertiary facilities. Its design follows from three findings established above: children present late, so the pathway must be triggered by early and non-specific features; paired cerebrospinal fluid and serum serology is the only indispensable investigation; and the three paraclinical modalities do not correlate with one another, so a normal result in any one cannot be used to close the diagnosis<sup>30</sup>.

**Table 8. Proposed resource-stratified diagnostic and management pathway for suspected paediatric SSPE.**

| Step       | Action                                                                                                                                                                                                                                    | Setting required |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 1. Suspect | Any child aged 0–18 years with progressive cognitive or behavioural decline, loss of acquired milestones, deteriorating school performance, new myoclonus, unexplained falls or new visual loss, whether or not measles or vaccination is | Any level        |

| Step                          | Action                                                                                                                                                                                                                                                                                                                                                                            | Setting required  |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
|                               | documented. Absence of a measles history does not exclude SSPE <sup>9, 8</sup>                                                                                                                                                                                                                                                                                                    |                   |
| 2. Core assessment            | Structured history recording date and documented source of each measles vaccine dose, age at each dose, and timing of any measles episode relative to the first dose; staged neurological examination; $\geq 30$ -minute awake and asleep EEG; paired CSF and serum measles IgG with albumin in both compartments; routine CSF cell count, protein, glucose and globulin fraction | District hospital |
| 3a. Low-resource pathway      | If the EEG is non-diagnostic and the clinical picture is compatible, repeat with sleep deprivation or benzodiazepine activation <sup>34, 35</sup> . If serology cannot be performed locally, transport paired samples to a reference laboratory rather than abandoning the diagnosis. Proceed on clinical grounds plus serology if imaging is unavailable                         | District hospital |
| 3b. Enhanced-resource pathway | Brain MRI with FLAIR, T2, diffusion-weighted and volumetric sequences for staging and exclusion; antibody index with albumin quotient; oligoclonal bands with band                                                                                                                                                                                                                | Tertiary centre   |

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| Step                  | Action                                                                                                                                                                                                                                                                                                                                                                                               | Setting required                |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
|                       | typing; CSF measles RT-PCR and genotyping for surveillance; video-EEG where myoclonus and complex coupling is uncertain                                                                                                                                                                                                                                                                              |                                 |
| 4. Classify and stage | Apply the modified Dyken criteria <sup>38</sup> ; assign the clinical stage; record stage at diagnosis explicitly, since it predicts outcome more strongly than any single investigation <sup>23</sup>                                                                                                                                                                                               | Any level                       |
| 5. Treat              | Begin established symptomatic care immediately: antiseizure and antimyoclonic therapy, swallowing assessment, nutritional plan, physiotherapy, respiratory care and early palliative involvement. Discuss investigational disease-modifying options honestly, and restrict intraventricular delivery to centres with neurosurgical support and capacity for aseptic repeated access <sup>47, 7</sup> | Any level; step-up for delivery |
| 6. Prevent and notify | Verify and complete the immunisation status of siblings and household contacts; notify the case to measles surveillance as a sentinel event; support catch-up immunisation in the affected community <sup>15</sup>                                                                                                                                                                                   | Any level                       |
| Red flags             | Status myoclonicus, rapid progression through stages within weeks, epilepsy                                                                                                                                                                                                                                                                                                                          | Any level                       |

| Step | Action                                                                                              | Setting required |
|------|-----------------------------------------------------------------------------------------------------|------------------|
|      | partialis continua, respiratory compromise or aspiration, or acute visual loss — refer the same day |                  |

#### Limitations and research priorities

This review is a structured synthesis rather than a systematic review with dual independent screening, and the frequencies quoted are unweighted across heterogeneous cohorts that were not pooled, because case definitions, referral patterns and denominators differ too widely to justify meta-analysis. Almost every cohort is hospital-based and therefore subject to referral bias. The therapeutic literature is dominated by uncontrolled series against a background spontaneous remission rate of 5–6%, and the single randomised trial was negative for clinical outcomes<sup>43</sup>.

Four priorities follow: denominator-anchored national estimates linking SSPE notification to measles surveillance; local re-derivation of enzyme immunoassay thresholds for paired cerebrospinal fluid and serum measles IgG, since the published framework rests on very few patients<sup>39</sup>; prospective evaluation of low-cost activation manoeuvres with a non-SSPE comparison group to establish specificity<sup>34</sup>; and formal pharmacokinetic studies defining the concentrations achieved in cerebrospinal fluid and brain tissue by each route, since the field's central failure has been delivery rather than molecular activity<sup>7</sup>.

#### Conclusion

SSPE is re-emerging wherever measles control has lapsed, now presenting in younger children with shorter latency and a more fulminant course. Age at measles infection is the dominant risk factor, and the timing of the first vaccine dose rather than eventual coverage determines how long infants remain susceptible. Diagnosis rests on intrathecally synthesised anti-measles IgG interpreted against locally derived assay thresholds; the periodic electroencephalographic complex is highly specific but often absent early and can frequently be elicited by inexpensive activation manoeuvres; and imaging stages the disease and excludes alternatives without ever confirming it. No disease-modifying therapy has established efficacy, and the reason is instructive for drug development: agents with convincing in vitro activity have failed by the oral route because they do not reach virustatic concentrations in the central nervous system, while the routes that do — intraventricular delivery through an implanted reservoir or pump — carry procedural risk and are unavailable to most children who develop the disease. Until a delivery strategy resolves that asymmetry, timely two-dose measles vaccination

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remains the only intervention of established effectiveness, and every incident case should be treated as a sentinel event.

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