Perinatal encephalopathy, the syndrome of intracranial hypertension and associated diagnostic labels in the Commonwealth of Independent States: a systematic review

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ABSTRACT

Background The WHO reports excessive rates of ill-defined neurological diagnoses and ineffective and potentially harmful drug treatments in children in the Commonwealth of Independent States (CIS). Collectively termed perinatal encephalopathy and the syndrome of intracranial hypertension (PE-SIH), these diagnoses are important contributors to perceived childhood morbidity and disability in the CIS. A systematic compilation of information on PE-SIH is lacking.

Methods We systematically reviewed publications between 1970 and 2020 on PE-SIH in Azerbaijan, English, Russian and Ukrainian languages and summarised information on PE-SIH.

Results We identified 30 publications (70% in Russian) published 1976–2017. The diagnosis of PE-SIH was either based on unreported criteria (67% of reports), non-specific clinical features of typically developing children or those with common developmental disorders (20% of reports) or cranial ultrasound (13% of reports). The reported proportion of children with PE-SIH in the study samples ranged from 31% to 99%. There were few published studies on reassessments of children diagnosed with PE-SIH, and these did not conform neurological disease in the majority of children. Treatments included multiple unlicenced drugs without established effectiveness and with potential unwanted effects.

Conclusion This review suggests that PE-SIH is a medical diagnostic label that is used in numerous children without substantive associated disease. The diagnosis and treatment of PE-SIH is a multidimensional, iatrogenic, clinical and public health problem in the CIS. With increasing use of evidence-based medicine guidelines in the region, it is hoped that PE-SIH will gradually disappear, but actions to accelerate this change are nevertheless needed.

INTRODUCTION

The United Nations Sustainable Development Goals include the integration of interventions to promote optimal development during childhood. To achieve this goal, health systems must be strengthened to address child development and to prevent non-evidence based practices. An excessive rate of ill-defined neurological diagnoses and the use of ineffective and potentially harmful medications to treat these conditions in countries of the Commonwealth of Independent States (CIS) has been a focus for the World Health Organization (WHO). The CIS refers here to the independent states that formed after the disintegration of the Soviet Union, comprising Armenia, Azerbaijan, Belarus, Georgia, Moldova, Kyrgyzstan, Kazakhstan, the Russian Federation, Tajikistan, Turkmenistan, Ukraine and Uzbekistan.

Problems in the management of children in three countries in the CIS were highlighted by a WHO observational study. Children with physical symptoms or behaviours seen in typically developing children frequently had been given inter-related diagnostic labels and treated with a wide range of medications. Many of these diagnoses could be grouped under the umbrella label ‘perinatal encephalopathy’ (PE) or ‘perinatal encephalopathy manifesting as the syndrome of intracranial hypertension’ (PE-SIH). The term PE was introduced to the Russian medical literature in 1976 by Iurii Iakunin, a Soviet paediatric neurologist, to denote a spectrum of conditions in neonates and infants attributed to brain injury originating in the

What is already known on this topic?

- Observations in countries and existing literature reports point to a high rate of poorly substantiated neurological diagnoses in children from the Commonwealth of Independent States countries.
- These diagnoses, collectively termed perinatal encephalopathy and the syndrome of intracranial hypertension (PE-SIH), are largely unknown and non-existent in Western medicine.

What this study adds?

- The terminology used and published literature provide evidence that there is no substantive disease in children diagnosed with PE-SIH.
- Children diagnosed with PE-SIH are being treated with multiple unlicensed drugs without established effectiveness and with potential unwanted effects.
perinatal period. The term PE-SIH has come to be subsequently applied to neonates and infants and to older children to indicate a neurodevelopmental disorder thought to have origins in the neonatal period. PE-SIH refers to clinical manifestations of a presumed increase in intracranial pressure from perinatal brain injury. ‘Hypertensive syndrome,’ ‘hypertensive-hydrocephalic syndrome’ and ‘hydrocephalic syndrome’ are closely related diagnostic labels, frequently used interchangeably with PE-SIH.

For brevity in this review, we shall use the term PE-SIH to refer to any of these diagnostic labels.

The literature indicates that in CIS countries, physicians may attribute various paediatric complaints to PE-SIH. PE-SIH does not exist in the WHO International Classification of Diseases (ICD). A novel classification system of perinatal nervous system injuries in infants devised by Russian perinatal medicine specialists in 2005 has aimed at merging PE-SIH with ICD-10 codes but has been criticised for the mismatch between the assigned ICD codes and the concepts that PE-SIH represents.

The diagnosis of PE-SIH, as described above, does not require direct assessment of intracranial or lumbar cerebrospinal fluid pressure and is unrelated to pseudotumor cerebri syndrome (PTCS), also known as idiopathic intracranial hypertension, which exists in the ICD. The diagnosis of PTCS requires assessment of cerebrospinal fluid pressure, has precise diagnostic criteria and is not a diagnosis of infancy.

The present review was undertaken to fill the existing vacuum in the published literature in English regarding the clinical context in which diagnostic labels related to PE-SIH have been employed, numbers of children diagnosed in studies and the treatments to which they have been exposed.

METHODS

Search strategy

We conducted a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement and included an online search of dissertations, textbooks, original articles and reviews written between January 1970 and January 2020 in Google Scholar, PubMed, the Russian bibliographic database eLIBRARY (elibrary.ru) and an open-access full-text resource CyberLeninka (cyberleninka.ru). The following search terms in English and Russian (shown as English translations within square brackets) were used: perinatal encephalopathy, syndrome of intracranial hypertension, hypertensive syndrome, hydrocephalic syndrome, hypertensive-hydrocephalic syndrome, [perinatal encephalopathy], [syndrome of intracranial hypertension], [hydrocephalic syndrome], [hydrocephalic-hydrocephalic syndrome]. The titles and abstracts of the retrieved entries in Azerbaijani, English, Russian and Ukrainian languages were reviewed by first and second authors, RM and TS-M. This review included reports if they involved children (aged 0–18 years) diagnosed with the search terms and any of the following: (A) numbers of children; (B) clinical features of the diagnoses; (C) assessments of diagnosed children; and (D) treatment. Reports involving only preterm or high-risk infants or children with PTCS were excluded. We supplemented the search by reviewing relevant references of the identified manuscripts. A systematic PubMed and Cochrane database search of published clinical trials involving drugs used in children with these diagnoses was performed using the following terms (medical subject heading or supplementary concept): 4-amino-3-phenylbutyric acid (phenIBUT), acetazolamide, Actovegin, bendazole, Cerebrolysin, choline alfoscerate, cytidine diphosphate choline (citicoline), cinnarizine, Cortenex, ethylmethylhydroxypropidine succinate, furosemide, ginkgo biloba, glycerylphosphorylcholine (choline alphoscerate), glycine, nicergoline, pantogab (calfum hormone), phenobarbital, piracetam, pyrithioxine, N-acetylaspartate, nicotinyl-GABA, thiazides (hydrochlorothiazide/triamterene) and vinpocetine. For publications reporting proportions of children with PE-SIH, we calculated 95% CIs for a population proportion using the Clopper-Pearson method. We were not able to undertake an assessment of potential publication bias.

RESULTS

An initial search identified 499 entries in PubMed, 136 in eLIBRARY, 1832 in Cyberleninka and 2540 in Google Scholar. After screening, 62 full-text publications were reviewed; 20 were found eligible. Ten other publications were identified through cited references making a total of 30 publications.

Clinical features and special investigations

The diagnosis of PE-SIH was reported to be based solely on clinical features in 6/30 (20%) of the publications, two of which were published in the last decade. The reported clinical features were predominantly non-specific symptoms (frequent crying, irritability, possetting, sleep disturbance, emotional lability, irritability, cutis marmorata, faltering growth, chin tremor, strabismus, motor or language delay and tip toe walking). Some signs were not mentioned as necessary for the diagnosis of PE-SIH and applied only to a minority of cases, although precise figures were lacking in the publications. Some publications reported that the PE-SIH diagnostic label in infants also can be based on a history of maternal syphilis, any illness during pregnancy, home birth or poor perinatal care.

The diagnosis of PE-SIH often was based entirely on clinical features; non-specific imaging abnormalities were cited as the basis of diagnosis in the absence of clinical features in 3/30 (10%) of the publications and in 4/30 (13%) the importance of ultrasound was emphasised. A 2016 practice guideline from the Russian Federation recommended in addition to cranial ultrasound, the use of dopplerometry and dopplerography, electroencephalography, cranial CT, MRI, fundus examination and hearing screening in the diagnostic work-up of children with PE-SIH. Of 15 studies reporting numbers of children with PE-SIH, one had used multiple cranial imaging modalities for clarification of the neurological status of children, six used medical history, cranial ultrasound, doppler ultrasonography and/or electroencephalography while eight did not report the diagnostic criteria and methods used.

Drugs used for the treatment of PE-SIH

Multiple drugs and other agents were used in the treatment of PE-SIH including anticonvulsants, cattle-derived neuropeptides and blood extracts, diuretics, nootropic and vasodilating agents, psychostimulants, mineral and metabolic supplements. Publications between 2004 and 2009 suggest that one-third of children with a diagnosis of PE-SIH were treated with a combination of up to four drugs. One study reported that infants ‘diagnosed with PE’...
and apparently healthy infants considered ‘at risk for PE’ were both receiving diuretics, nootropics (so-called cognitive enhancers), vasoactive drugs and sedatives. \textsuperscript{22}

**Numbers of children diagnosed with PE-SIH**

Table 1 summarises studies published between 1997 and 2010 that report on numbers of children with PE-SIH. All studies were retrospective reviews of medical records, four on children attending outpatient clinics and one on children born in the studied hospital. \textsuperscript{22,23,28,31,32} The percentage of children diagnosed with PE in these clinical populations ranged from 33\% to 99\%. Five other studies reported samples from orphanages \textsuperscript{24} or adoption clinics. \textsuperscript{21,29,30} The PE-SIH rate in these special settings ranged from 31\% to 100\%. None of these studies have population-based samples.

**Reassessment of children diagnosed with PE-SIH**

Several studies reported on the outcomes of children with PE-SIH on their independent assessment or reassessment when older. A study from the Russian Federation published in 2009 reported that in a paediatric outpatient population of 800 infants aged 3 months, 744 (93\%) had received a diagnosis of PE-SIH, but 584 (73\%) lacked neurological abnormalities when they had outgrown infancy. \textsuperscript{22} Three studies reported on detailed independent evaluations of children that had received the diagnosis of PE-SIH. \textsuperscript{31,32} Miller in 2005 reported on 107 children of which the majority were diagnosed with PE-SIH in Eastern Europe and the Russian Federation and their paedoptative evaluations in international adoption clinics in the United States of America (Table 1). \textsuperscript{24} None of these children was found to have a specific neurological disorder. In a study by Tatochenko et al. \textsuperscript{12} from the Russian Federation in 2006, a team of paediatric neurologists re-evaluated 162 infants diagnosed with PE-SIH among 185 infants attending two primary care clinics in Moscow. In 149 (92\%) children, no abnormality was seen; 13 (8\%) had a neurological disorder including ‘vegetative visceral syndrome’ (an entity not recognised by the ICD), cerebral palsy, developmental delay, kernicterus, hydrocephalus or microcephaly.

**Discussion**

This literature review suggests that PE-SIH is a medical entity that is conceptually different from diagnostic categories used in ICD-10 and often not associated with a substantive underlying neurodevelopmental disorder. The practice of labelling children in this way may have important negative consequences for individual children, families and society at large.

A strength of this review is that it includes publications in Russian, which is the predominant scientific medical language in CIS countries. There are a number of limitations of the study. First, we cannot exclude publication bias and it is impossible to extrapolate the data with any confidence to a population prevalence. Second, the unavailability of online library-based biomedical databases in Russian limited the extent to which the search could be exhaustive with keywords. Third, intercountry comparisons were not possible because of the lack of comparable data from the different nations.

In Western paediatric neurology, acute neonatal encephalopathy, often shortened to neonatal encephalopathy (NE), is a clinical—not aetiological—term that indicates a short-term neonatal clinical state including alteration of the level of consciousness. \textsuperscript{35} Seizures, abnormalities of muscle tone and of other aspects of the neurological examination may be present with or without difficulties in respiratory control and feeding. \textsuperscript{35,36} The most common of several possible aetiologies is hypoxic-ischaemic encephalopathy, while metabolic disorders, infections, drug exposure, stroke and congenital malformations are other well-recognised aetiologies. \textsuperscript{35} The longer term sequelae that may follow NE are usually denoted by different diagnostic labels (eg, cerebral palsy), and the child does not continue to carry the diagnosis or the label of NE. The global incidence of (acute) NE is 8.5 per 1000, \textsuperscript{36} which is much lower than the diagnostic rates for PE (33\%–99\%) reported in the literature identified by this review. \textsuperscript{22,23,28,31,32} Because none of these studies have population-based samples, these rates do not provide estimates of prevalence, but the numbers reported give a sense of the scale of the use of PE-SIH as a diagnostic label. Pal’chik and Shabalov\textsuperscript{8} have proposed the following reasons related to health systems for the high prevalence of PE-SIH. These include diagnostic uncertainty (arising from lack of familiarity with standard neurological examinations, typical variations in child behaviour or development, and/or classifications of neurological disorders) and issues related to health systems (eg, lack of legal, administrative and ethical consequences of malpractice, justification of staffing levels by reference to high prevalence of diagnosed disorders and, in the private sector, financial benefit to physicians). There might be, in addition, a degree of demand from parents anxious for a diagnostic label and for the reassurance of prescribed treatment. \textsuperscript{8,37}

The use of diagnostic entities indicating perinatal injury to the nervous system beyond the neonatal period and without corroborating findings or investigations has been criticised in scientific publications from the Russian Federation\textsuperscript{8,13,11} and in popular articles written for parents on websites of respected physicians. \textsuperscript{8,39} Despite this, scientific articles and textbooks published from 2009 to 2017 continue to mention that the prevalence of PE-SIH is high, attribute diagnostic value to a wide variety of nonspecific symptoms in infants diagnosed with PE-SIH based on history and ultrasonography alone and recommend drug treatments most of which have no scientific rationale. \textsuperscript{7,9,13,15,25}

Studies that have relied on cranial ultrasonography for the diagnosis of PE-SIH in infants have attributed diagnostic value to the increased dimensions of the cerebral ventricles, but normative reference data for these parameters are available only for newborns (eg, lateral cerebral ventricular index or anterior horn width) or are entirely lacking (eg, third ventricular or interhemispheric fissure width). \textsuperscript{40}

The impacts of the diagnostic label of PE-SIH and associated drug treatments for presumed intracranial hypertension or brain injury on children with non-specific symptoms are multiple and include potential adverse effects of drug treatments. \textsuperscript{3,4,8,10,11,37} Most of the drugs used in infants and children diagnosed with PE-SIH are not licenced by the European Medicines Agency (www.ema.europa.eu) or the US Food and Drug Administration (www.fda.gov) and have not been evaluated with rigorous randomised controlled trials. These drugs lack evidence of long-term therapeutic benefit even in the case of infants with established perinatal brain injury. \textsuperscript{41–48} and some have well-documented unwanted effects.

The diagnosis of PE-SIH may also cause harm by contributing to a failure to diagnose other disorders, for example, autism, cerebral palsy, epilepsy, language delay or hearing/visual impairment. Furthermore, children with the diagnosis of PE-SIH may be subject to unwarranted follow-up appointments, diagnostic procedures and hospital admissions. \textsuperscript{4,8,37} A less well-recognised complication may be the development of the vulnerable child syndrome. \textsuperscript{49} This occurs in children who have been diagnosed with a possible illness early in life, leading to them
# Table 1 Summary of publications related to perinatal encephalopathy, the syndrome of intracranial hypertension and other diagnostic labels relating to the same clinical phenomena in the Commonwealth of Independent States and Eastern European countries

<table>
<thead>
<tr>
<th>Study author and year</th>
<th>Sample</th>
<th>Methodology</th>
<th>Terminology used in the medical records or publication</th>
<th>% (95% CI)* of study sample diagnosed as PE-BH</th>
<th>N affected in study population</th>
<th>Diagnosed neurological conditions on independent re-evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical populations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khotkova et al. (2009)</td>
<td>Infants attending outpatient clinics in Nizhnij Novgorod, Russian Federation</td>
<td>Outpatient medical record review.</td>
<td>Perinatal encephalopathy.</td>
<td>8.3% of 800 infants at 1 month of age</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tatarchenko et al. (2006)</td>
<td>Infants attending outpatient clinics in Moscow, Russian Federation.</td>
<td>Outpatient medical record review.</td>
<td>Perinatal encephalopathy.</td>
<td>87.6 (82.8 to 92.3)</td>
<td>162/185</td>
<td>149 out of 162 (92.0%) diagnosed had no neurological pathology, 13 (8.0%) were diagnosed with disorders including central palsy, developmental delay, hernia, hydrocephalus, microcephaly and vegetative-visceral syndrome.</td>
</tr>
<tr>
<td>Davydov et al. (2016)</td>
<td>Infants born 2002–2004 who had health supervision visits at a single primary healthcare centre in Kemerovo, Russian Federation.</td>
<td>Not specified.</td>
<td>Perinatal encephalopathy.</td>
<td>98.5 (98.2 to 98.8)</td>
<td>368/373</td>
<td>N/A</td>
</tr>
<tr>
<td>Fedorov and Salamova (2009)</td>
<td>Infants attending district outpatient clinics in Moscow, Russian Federation.</td>
<td>Outpatient medical record review.</td>
<td>Perinatal encephalopathy.</td>
<td>67.4 (57.9 to 76.8)</td>
<td>180/37</td>
<td>N/A</td>
</tr>
<tr>
<td>Miller et al. (2007)</td>
<td>Children in Murmansk orphanages, Russian Federation.</td>
<td>Medical record review.</td>
<td>Perinatal encephalopathy.</td>
<td>46% of infants and 31% of older children in a sample of 193 children.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Miller (2005)</td>
<td>Children being considered for international adoption from the CIS countries and Eastern Europe.</td>
<td>Medical record review conducted by International Adoption Clinic in the USA.</td>
<td>Perinatal encephalopathy.</td>
<td>69.2 (59.5 to 79.7)</td>
<td>14/107</td>
<td>Except for developmental delay, hypotonia and microcephaly, no other condition has been identified.</td>
</tr>
<tr>
<td>Yulish et al. (2010)</td>
<td>Comparative study of three groups of children under 5 years of age from Donetsk, Ukraine, method of sampling is not reported. Group 1: from orphanages. Group 2: children with frequent upper respiratory tract infections. Group 3: children considered healthy.</td>
<td>Retrospective medical record review.</td>
<td>Perinatal encephalopathy.</td>
<td>8.5 (2.4 to 20.4)</td>
<td>2/107</td>
<td>N/A</td>
</tr>
<tr>
<td>Jenista (2000)</td>
<td>Children being considered for international adoption. 2422 (88% of 2814 records) were from Eastern Europe and Russian Federation.</td>
<td>Medical record review conducted by International Adoption Clinic in the USA.</td>
<td>Perinatal encephalopathy.</td>
<td>53.2 (38.9 to 67.5)</td>
<td>25/47</td>
<td>No severe neurological condition diagnosed. Brachial plexus injury, chronic hepatitis B, fetal alcohol syndrome, hydrocephalus, mild spastic paraparesis, myelomeningocele, optic nerve hypoplasia, orthopaedic problems, polydactyly, strabismus and unilateral hearing loss have been identified.</td>
</tr>
<tr>
<td>Albers et al. (1997)</td>
<td>Children being considered for international adoption from the CIS countries and Eastern Europe.</td>
<td>Medical record review conducted by International Adoption Clinic in the USA.</td>
<td>Perinatal encephalopathy.</td>
<td>8.5 (2.4 to 20.4)</td>
<td>4/47</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*95% CI has been calculated using reported figures where available. **Although these diagnostic labels have been listed separately, they all refer to the same clinical phenomena.**

CIS, Commonwealth of Independent States; N/A, not available; PE, perinatal encephalopathy; PE-SIH, perinatal encephalopathy and syndrome of intracranial hypertension; USA, United States of America.
being perceived by their parents as weak and vulnerable.\textsuperscript{49} The vulnerable child syndrome is associated with separation anxiety, out-of-control behaviour, school underachievement, lowered self-esteem and restricted physical activity in childhood and excessive use of healthcare in adulthood.\textsuperscript{49} Children labelled as having PE-SIH are falsely diagnosed with a possible illness early in life, and the psychological effects of the diagnosis of PE-SIH such as the potential for the vulnerable child syndrome require further study.

There is also a public health burden resulting from the diagnosis of PE-SIH being incorrectly cited as a contraindication or reason for deferral of vaccinations. Vaccination rates have dropped as low as 50% in the Ukraine in the last decade,\textsuperscript{50} and the impact of diagnoses in the PE-SIH spectrum on vaccine hesitancy in the region requires further investigation.

The WHO, in its 2007 report of an intercountry technical consultation in St Petersburg on the topic of the management of neurological conditions in children, acknowledged that ‘in many countries there have already been some encouraging improvements in the management of common neurological conditions in newborn infants as a result of WHO action aimed at improving perinatal care through on-the-job training and joint revision of clinical guidelines for neonatal care.’\textsuperscript{5} Further efforts should include pre-service and in-service training programmes on evidence-based medicine, current concepts of early childhood development and the Nurturing Care Framework,\textsuperscript{21} and guidance on how best to support families in their efforts to help children to achieve their full neurodevelopmental potential.

Established practices may take time to change, but more rapid changes at a national healthcare level are also relatively achievable in the centralised healthcare systems of the CIS countries. Georgia has developed modern systems to address early childhood development and disability.\textsuperscript{52} In the Russian Federation, a recent update of a highly regarded textbook has highlighted the need to address the issue of PE-SIH, and public health authorities have advised clinicians that the diagnosis of PE-SIH should not in itself serve as a contraindication to vaccination.\textsuperscript{4, 53} In Azerbaijan, the ministry of health has recently advised against the diagnosis of PE-SIH because ‘it does not exist in the ICD system’. These encouraging developments and the current WHO initiative of ‘Child Health Redesign’ for the 40th anniversary of the Alma Ata declaration provide an opportunity to maintain momentum, update concepts and unify a conceptual framework for use by child healthcare providers, which is based on ICD.\textsuperscript{54}

CONCLUSION

The diagnosis and treatment of PE-SIH is a multidimensional iatrogenic, clinical and public health problem with negative impacts on children, families, society and the practice of paediatrics in the CIS countries. As evidence-based medicine and clinical practice guidelines are increasingly being introduced in these countries, this problem should diminish, but further actions by health systems to accelerate improvements are needed.

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