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Review article

Neurological complications in childhood nephrotic syndrome: A systematic review

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ABSTRACT

Background and objective: Nephrotic syndrome (NS) in childhood can be accompanied by serious neurological complications increasing the morbidity of disease. The study aimed to assess the spectrum of neurological complications in children with in terms of clinical presentation, contributory risk factors, and outcome.

Methods: In this systematic review, we searched for articles in PubMed, providing individual patient-level data for any neurological complication in children and adolescents with primary NS, between January 1, 1990 and April 30, 2018.

Findings: The search yielded 63 articles, involving 103 patients. Events occurred more frequently during nephrotic state relapses; 71.6% of cerebral thromboembolic (TE) events and 81.2% of posterior reversible encephalopathy (PRES) cases. Median duration of disease before a cerebral TE event was 3 months (IQR 0–27), and 18 months (IQR 1-37.5) for PRES. Among cases with TE, 73.1% presented with cerebral sinovenous thrombosis (CSVT), and 16.9% parenchymal lesions. 70% of patients had a risk factor for neurological complication including NS-associated thrombophilia, hypertension, and treatment with immunosuppressive agents. Outcome was favorable in 93.8% of the patients with PRES. In patients with cerebral TE outcome was favorable in 95.8% of the cases with CSVT only, and in 64.7% of the cases with parenchymal lesions.

Conclusions: Neurological complications may occur in children with primary NS and risk factors during nephrotic state relapses. The outcome for PRES has been reported favorable. Outcome in cerebral TE events may differ by the presence of venous or artery infarct. Recognition of additional protrombotic state risk factors may help to lower the incidence of neurological complications.

Abbreviations: NS, Nephrotic syndrome; TE, Thromboembolism; PRES, Posterior reversible encephalopathy; CSVT, cerebral sinovenous thrombosis; LMWH, low molecular weight heparin.

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Contents

1. Introduction

Nephrotic syndrome (NS) is one of the most common causes of chronic kidney disease in childhood[1] with an incidence of 2-7 per 100,000 children. NS is characterized by heavy proteinuria, hypoalbuminemia, generalized edema and hypercholesterolemia. Significant complications may occur during the course of NS, including infection, bone mineral loss, acute kidney injury and cardiovascular and neurological disease. The most commonly reported neurological complication is cerebral thromboembolism (TE), which remains one of the most serious and life-threatening events.[2,3] Posterior reversible encephalopathy syndrome (PRES) is another frequently reported neurological complication in children with NS[4].

Most data on neurological complications in childhood NS are based on cases reports, whereas there are limited numbers of case series. In the absence of high quality evidence, decision-making and recommendations on how to manage these children are based on expert opinion. The aim of this review was to systematically assess the spectrum of neurological complications in children with primary NS, examining demographics, clinical data, imaging findings, contributory risk factors, and outcome.

2. Methods

2.1. *Search strategy, selection criteria and quality assessment*

We performed a literature search in PubMed using key words "nephrotic syndrome", and "children" or "adolescents", and "stroke" or "sinovenous thrombosis" or "cerebral thrombosis" or "stroke" or "posterior reversible encephalopathy syndrome" or "reversible posterior encephalopathy syndrome" or "hypertensive encephalopathy" or "neurological complication", between January 1, 1990 and April 30, 2018. In addition, we manually examined the reference lists from related articles. Articles published in English or French language were examined.

Eligible studies were full-text articles presenting data from observational studies, case reports or case series, including children and adolescents up to 18 years of age with primary NS, which provided individual patient-level data description of any neurological complication. Two independent investigators (SS and KC) screened titles and abstracts. Then, studies passing title and abstract screening were subjected to full text review, independently performed by the two investigators. Cases of disagreement were resolved by a third investigator (DZ).

Study methodological quality assessment was performed by a modified version of a published tool for evaluating case reports or case series.[5] Two investigators (SS and KC) independently assessed the study quality. Studies were rated in 3 domains: a) Selection (the cases represent the whole center's or investigators' experience), b) Ascertainment of exposure and outcome (accurate diagnosis, long enough follow-up) and c) Reporting (cases described with sufficient details with regard to clinical presentation, history, laboratory and imaging findings, treatment, and outcome).

2.2. *Data extraction and analysis*

For each patient, reported in the literature demographic data, clinical information with regard to NS course, NS type and histopathology, neurological symptoms, laboratory and imaging findings, treatment, and outcome were extracted. Data were presented using standard descriptive statistics, means (±standard deviation, SD) or median (interquartile range, IQR) for continuous variables, and as percentages for categorical variables. The Stata 12.0 software was used for the analysis.

3. Results

3.1. Publication characteristics and quality

A total of 106 articles were retrieved after database and manual search (Fig. 1). Sixty-six were assessed for eligibility and 3 were removed because they did not provide individual patient-level data. The remaining 63 studies were included in the review, 38 reporting cases of cerebral TE, 22 cases of PRES, and 4 other rare neurological complications (Fig. 1). One study reported ≥1 neurological complications. Study quality was rated separately for cerebral TE and PRES articles. Selection was rated good for all articles. Ascertainment was rated 92.1% good, 5.2% fair, and 2.6% poor in articles reporting cases of TE, 94.7% good, and 5.2% fair in those of PRES cases. Reporting was rated 83.5% good, and 13.2% fair in articles reporting cases of TE, and 77.3% good, and 22.7% fair in those of PRES cases.

3.2. Cerebral thromboembolism

We identified 67 cases of cerebral TE in children with primary NS, either reported as single case reports or as cases series (Appendix A, Supplementary table A.1.). Mean age at presentation of cerebral TE was 7.24 ± 4.31 years (range: 2 months-18 years). There was a predominance of male patients (70.1%). Cerebral TE occurred on initial presentation of NS in 19/67 (28.4%) of cases; 48/67 (71.6%) of TE's occurred during disease relapse, 32/48 (66.7%) of cerebral sinovenous thrombosis (CSVT), and 15/17 (83.3%) of arterial ischemic strokes. Median disease duration from NS diagnosis to development of cerebral TE was 3 (IQR 0–27) months; 3 (IQR 0–17.5) months for CSVT, and 8 months (IQR 0.2–93) for arterial ischemic stroke. Information on NS type was available in 35 cases; 11 were steroid sensitive, 13 steroid-dependent and 11 steroid-resistant. Histopathology was reported in 22 cases; 11/22 showed focal segmental glomerulosclerosis (FSGS).

The most common clinical manifestations in NS-associated cerebral TE are presented in Table 1. Of 67 cases, 49 (73.1%) had solely CSVT, 12 (17.9%) had solely parenchymal lesions due to cerebral arterial thrombosis, and 6 (9%) had both CSVT and parenchymal lesions. CSVT occurred more commonly in the superior sagittal sinus (46/55, 83.6%), the transverse sinus (27/55, 49%), the straight sinus (14/55, 25.4%) and the sigmoid (9/55, 16.3%), sinus; multiple sinuses were involved in more than half of the cases (30/55, 54.5%). In most cases of arterial ischemic stroke, the parietal and occipital lobes, the cerebellum and the thalamus were affected. Multifocal cerebral arterial infarcts were commonly reported. In addition, three cases of non-cerebral TE (two pulmonary embolism, one renal artery thrombosis) occurred simultaneously with cerebral TE. Brain CT was the initial imaging study in most cases, followed by MRI and MRV, MRA when available. Initial non-enhanced brain CT failed to diagnose cerebrovascular thrombosis in eight cases.

Table 2 shows additional risk factors for thrombosis in pediatric cases with NS and cerebral TE. Based on 50 cases with individually described risk factors, 35/50 (70%) had a risk factor for thrombosis; 26/39 (66.7%) of those with CSVT, 6/6 (100%) of those with arterial ischemic stroke, and 3/5 (60%) of those with both venous and arterial infracts. Thorough work up or genetic tests for thrombophilia have not been systematically performed in the patients. Inherited thrombophilia was investigated in some reports and positive findings were reported in 8 patients in the literature; MTHFR mutations in 5 cases, factor V leiden mutations in 2 cases, plasminogen activator inhibitor-1 (PAI) polymorphisms in 2 cases, and protein S mutation in 1. Severe proteinuria and hypoalbuminemia were present in the majority of cases. Mean serum albumin was 1.82 ± 0.48 mg/dl. Multiple risk factors were present in about 40% of the cases.

Standard unfractioned heparin or low molecular weight heparin (LMWH) were initially administered in the majority of cases, followed by oral anti-coagulants in more than 50% of cases. The duration of treatment was variable ranging from few weeks to 6 months. No bleeding complications related to treatment have been reported. In two cases, systemic thrombolysis was performed with favorable outcome.

Reported neurologic outcome was favorable in 87.7% of the cases with data on outcome; in 46/48 (95.8%) of CSVT cases compared to 11/17 (64.7%) with parenchymal lesion with or without coexistence of CSVT. One patient died because of pulmonary embolism. None of the patients were reported to experience a recurrence of cerebral TE event.

3.3. Pres

We identified 32 cases of PRES in children with primary NS, either reported as single case reports, or cases series (Appendix a, Supplementary table A.2.). Mean age at presentation was 8.13 ± 4.19 years (range 1.5–17 years); 43.8% were males. PRES developed during initial presentation of disease in only 6/32 cases. Median duration of NS at event was 18 (IQR 1–37.25) months. Information on NS type was available in 18 cases; 12 were steroid-resistant. Histopathology was available in 14 cases with 9 showing FSGS.

Clinical symptoms are summarized in Table 1. In most cases, the diagnosis was confirmed by brain MRI. In some cases, diffusion weight imaging (DWI) with apparent diffusion coefficient (ADC) mapping was further performed. In two cases, diagnosis was based on brain CT findings. Characteristic hyperintense areas on MRI were located in the parietal-occipital (24/32, 75%) temporal (8/32, 25%) and frontal lobes (7/32, 21.9%). Less frequent locations included basal ganglia, brain stem and cerebellum (only 3 cases).

Hypertension was reported in 71.9% of cases (Table 2). Eighteen patients (56.3%) were receiving calcineurin inhibitors, with 16 being on cyclosporine-A and 2 on tacrolimus. In 15 cases, hypertension and calcineurin inhibitor treatment were coexistent, while 16/32 (50%) had multiple (≥3) of the above risk factors present.

PRES management included antihypertensive medication and cessation of calcineurin inhibitor in the majority of cases. In 2 cases, cyclosporine-A was continued with good outcome. Anti-seizure medication was also administered in cases presenting with seizures. Decompressive craniotomy of the posterior fossa and ventricular drainage was performed in one patient with congenital NS presenting with hydrocephalus, and upward transtentorial herniation.

Outcome was favorable in 30/32 (93.8%) of the patients. One case developed chronic epilepsy and hippocampal sclerosis 3 years later, although MRI findings one month after PRES were reported normal. In a second case, aggressive behavior was reported after recurrence of PRES. Recurrence of PRES occurred in 4 cases at 1, 6, 7 and 8 months after the initial insult.

3.4. *Other rare neurological complications*

In one NS case with PRES, Wernicke's encephalopathy occurred almost concomitantly.[6] A case of diffuse cerebral hypoperfusion was reported in a one-year-old boy, which dramatically resolved when the nephrotic syndrome remitted.[7] Two children with nephrotic syndrome associated with Guillain-Barre syndrome have also been reported.[8,9] In both cases, Guillain-Barre syndrome preceded the presentation of NS and favorable neurological outcome was reported. Finally, a case of 3 year-old patient with stenotic kinking of left internal carotid artery resulting in ischemic left brain hemisphere infraction and followed by severe neurologic sequelae has been described. The patient was in NS remission receiving treatment with cyclosporine-A, and an adverse vasoconstrictive effect of the drug was assumed.[10]

4. Discussion

The current review showed that the most commonly reported NS-associated neurological complications in pediatric population are cerebral TE and PRES, presenting most frequently during nephrotic state. Risk factors evolving during the course of disease have been reported in the majority of pediatric patients with neurological complications. In most cases, the outcome for PRES has been reported favorable. However, outcome in cerebral TE events differed by the presence of venous or artery infarct.

The incidence of TE complications in children with NS has been traditionally considered lower (1.8–5.3%), than in adults (26.7%).[2] Divekar et al. reported only one case of CSVT among 700 cases of children with NS 30 years ago.[11] During the years 1992–2004, 85 cases of CSVT have been identified in Toronto based on the Canadian Pediatric Ischemic Stroke Registry; 4 cases were associated with idiopathic NS.[12] In another case

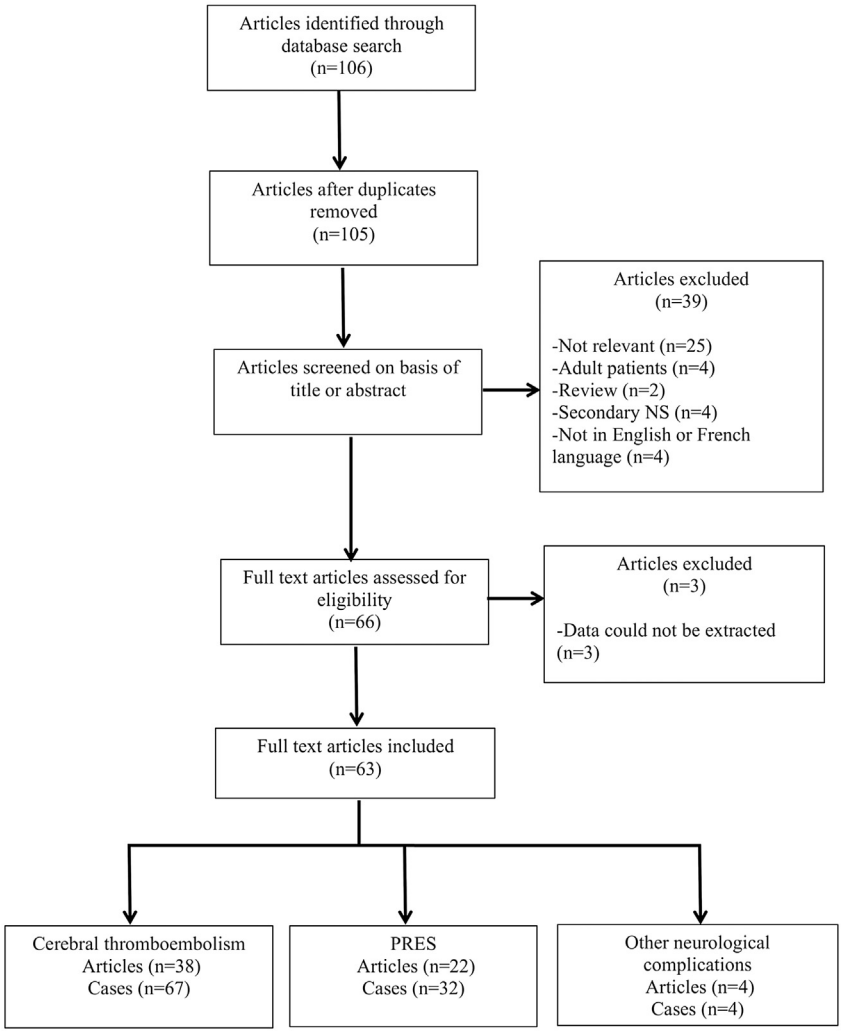

Fig. 1 – Study selection.

Table 1 – Common clinical manifestations in NS-associated cerebral thromboembolism and PRES.

Clinical Symptoms	n (%)
Cerebral thromboembolism	
Headache	34/67 (50.7%)
Vomiting	30/67 (44.8%)
Seizures	23/67 (34.3%)
Lethargy or altered consciousness	16/67 (23.9%)
Papilledema	9/67 (13.4%)
Hemiparesis	11/67 (16.4%)
Cranial nerve palsy	9/67 (13.3%)
PRES	
Seizures	23/32 (71.9%)
Altered consciousness	20/32 (68.8%)
Visual Impairment	16/32 (50%)
Headache	14/32 (43.8%)
Vomiting	7/32 (21.9%)

series study, among 188 children with idiopathic NS, 17 (9%) experienced a TE event.[3] The most recent case series from a tertiary center included 34 children with TE in a 6 years period.[13]

In the present review, the mean age of presentation of cerebral TE complication was 7.24 ± 4.31 years. Similar to previous reports, in most cases, the cerebral TE complication occurred during a disease relapse.[3,12] The event occurred early in the course of NS, with 3 months median disease duration from diagnosis to development of cerebral TE of, extending previous data on early occurrence of TE cerebrovascular events.[2] Of note, duration of disease was longer for those with arterial infarcts. CSVT occurred more frequently (73.1%) than cerebral arterial thrombosis (17.9%).[3,12,13] Superior sagittal sinus constituted the most common thrombosis location compared with other cerebral venous sinuses, possibly because it is a low-pressure location with no valves and the cerebral veins flow into the superior sagittal sinus in an oblique angle.[14] In most cases, the diagnosis of CSVT can be made on the basis of CT findings as it demonstrates direct signs of thrombosis (cord sign, dense triangle sign, or empty delta sign), edema, cerebral infarction, or parenchymal hemorrhage. However, conventional CT may miss the diagnosis of CSVT in up to 40% of children and underestimate both the extent of the thrombus and the presence of venous infarcts.[15] Brain MRI with MRV is considered to be the method of choice for the diagnosis of childhood stroke, visualizes flow and thrombus and is sensitive to parenchymal changes.

Table 2 – Risk factors for NS-associated cerebral TE and PRES.

Risk Factor	n of cases
Cerebral thromboembolism	67[a]
Hypoalbuminemia	33
Anti-thrombin III	13
Fibrinogen	6
Functional protein S deficiency	4
Thrombocytosis	3
Inherited thrombophilia	8
Infection	9
Dehydration	6
Hypertension	4
Lp(a)	3
PRES	32
Hypertension	23
Calcineurin inhibitors	18
Steroids	18
Generalized edema	18
Renal impairment	8

[a] Data on risk factors were available on 50 cases.

In the present review, over half of patients had a risk factor for thrombosis, especially those with cerebral arterial thrombosis. Consistent with previous studies, the most consistently reported coagulation abnormality was a decrease in anti-thrombin III level.[3,12] Alterations of coagulation and fibrinolysis system during active disease are considered the major mechanism associated with the increased risk of TE in patients with NS.[16–19] The few studies that examined directly the link between these derangements and TE, included small sample sizes, and had retrospective design. It is unclear whether the coexistence of inherited thrombophilia in NS could increase the risk for thromboembolism.[16] An adult study including 51 newly diagnosed patients with primary NS, reported that six (11.8%) had TE at time of diagnosis (4 symptomatic, 2 subclinical), all of whom carried mutations for either the prothrombotic factor V Leiden, prothrombin or methylene-tetrahydrofolate gene.[20] In the present review the number of cases, in which inherited thrombophilia was investigated, is low and did not allow assessing for any association. Hypoalbuminemia, present in the majority of cases in the literature, has been considered a major risk factor for NS associated TE events. Lipoprotein (a) described to act as inhibitor of fibrinolysis[12,16] has been reported in 3 cases. In a cohort of 49 pediatric patients with cerebral venous thrombosis, the combination of a prothrombotic risk factor with increased Lp(a) represented an independent 4.1 times increased risk of cerebral venous thrombosis.[21] Finally, drugs widely used in NS may associate with hemostatic abnormalities. Platelets contain a glucocorticoid receptor, and prednisolone has been shown to have a regulatory effect on platelet function in vitro.[22] Steroids may also raise the concentration of several clotting factors, principally factor VIII and von Willebrand or decrease the fibrinolytic activity reflected specifically by elevated plasma concentration of PAI1.[23] Moreover, diuretics abuse may lead to volume depletion and hemoconcentration favoring the development of TE complications.[12]

The outcome of CSVT was superior to those with parenchymal lesion with or without coexistence of CSVT. Cerebral TE complications most frequently occurred in veins than arteries, resulting in favorable outcome in the cases totally. The absence of profound atherosclerotic disease, compared to adults, may favor the prognosis in childhood NS associated-TE.[24] Anticoagulation, by unfractioned heparin in earlier or LMWH in more recent cases, was administered as first line treatment in the majority of the patients. Despite similar treatment practices in acute phase, the duration of treatment was variable and do not allow assessment of associations between treatment and outcome. The data with regard to treatment of cerebral TE complications in children with NS are limited and evidence-based recommendations are lacking.[18] The American College of Chest Physicians guidelines suggest that a child with a first venous TE should receive an initial minimum 3–6-month

course of anticoagulation.[25] There are few case reports on thrombolytic therapy in children with primary NS and cerebral TE, supporting the safety and efficacy of streptokinase and tissue plasminogen activator as treatment options.[26,27] The main challenge remains to establish criteria about prophylactic anticoagulation therapy in children with NS-associated TE.

PRES has been reported with a high frequency in children with kidney diseases.[4] Kwon et al. found a 50% prevalence of underlying NS among pediatric cases presenting with PRES.[28] In a retrospective single-center study of children with kidney diseases, 8% (5/87) of the patients with NS under cyclosporine A treatment presented with PRES.[29] However, in another retrospective study, Onder et al., reported only 1 patient with NS among 18 children with kidney diseases and PRES diagnosis.[30] The mean age of PRES presentation in NS pediatric cases in the present review was 8.13 years, lower than the age of patients with PRES and kidney diseases reported in single institution studies.[28,31,32]

PRES typically affects subcortical white matter in the parieto-occipital lobes, possibly because the posterior circulation is more vulnerable to hyperperfusion during BP elevation, which may be due to reduced sympathetic innervation.[33] Gray matter and regions other than the parieto-occipital lobes, including frontal, temporal lobes, basal ganglia, cerebellum, and brain stem, were less frequently involved.[34–36] CT may be useful on initial presentation to differentiate from intracranial hemorrhage, especially in unstable patients, and may be more readily available than MRI. However, brain MRI is considered the gold standard for the diagnosis of PRES.[4] Diffusion weight imaging with apparent diffusion coefficient mapping has been considered useful to predict outcomes and follow the pathophysiologic changes during the course of PRES.[4,29]

Acute and/or severe hypertension causes vasogenic edema, either by hyperperfusion due to cerebrovascular autoregulation failure, or hypoperfusion due to cerebral artery vasoconstriction, brain ischemia, leading to increased vascular permeability.[4] Notably, in 1/3 of cases PRES developed in patients with normal BP levels. Calcineurin inhibitor therapy with cyclosporine-A or tacrolimus, has been suggested as another important predisposing factor for the development of PRES causing vascular endothelium damage, followed by release of vasoactive agents, and finally leading to vasogenic edema. Studies have shown that PRES may develop in patients on calcineurin inhibitor treatment with drug levels within the therapeutic range.[29,31] The majority of patients with NS presented with hypoalbuminemia and severe generalized edema, suggesting increased vascular permeability. In addition, they were usually hypertensive and about half of the cases received calcineurin inhibitors. Steroid treatment in high doses and renal failure presenting with PRES, have been suggested not only to exaggerate blood pressure elevation, but also to have a causative role.[31,33] Zhou et al., in a retrospective study that included children with NS, 21 with PRES and 30 without PRES, found that PRES patients exhibited higher rates of calcineurin inhibitor and high-prednisone treatment, higher systolic blood pressure and lower albumin levels.[29] Finally, T cell activation and inflammatory cytokine production have been suggested as additional predisposing factors for PRES in NS patients in whom inflammatory factors may exist, especially during relapses.[31,33]

Supportive therapy and removal of predisposing factors were the main treatment modalities in NS pediatric patients with PRES. However, in two cases treated with calcineurin inhibitors, the administration of drug was continued, balancing cost of severe, not responding nephrotic state, to harm from treatment. The outcome was favorable in these cases, as well to those with re-administration of calcineurin inhibitor after resolution of PRES.[31,37,38] Multiple PRES episodes have been reported in some cases, but no certain profile of these patients predisposing to disease recurrence could be established.[6,39,40]

The results of the present systematic review should be interpreted taking into account potential limitations. The absence of high quality studies such as any prospective case control studies comparing different histopathology types or disease associated risk factors children with and without neurological complications, or studies comparing the effect different treatment modalities in patients with neurological complications could not allow performing data analysis and risk assessment in terms of a meta-analysis. The results of the present systematic review may not generalize and should be confirmed by future prospective studies. However, the strength of the present systematic review is the comprehensive investigation of all the available data on neurological complications in children and adolescents with NS, providing systematic evidence for timing of event presentation, risk factors, and outcome.

5. Conclusions

Nephrotic state in children confers a high risk for neurological complications. The clinical profile of pediatric patients with severe nephrotic state may include low serum albumin, generalized edema, hypertension, calcineurin inhibitors and high dose steroid treatment, and possibly acute or chronic renal injury, all constituting predisposing risk factors for cerebral thrombosis or PRES. However, none of these conditions has been independently associated with the occurrence of neurological complications, neither with their outcome in prospective studies. Focus on additional trombophylic risk factors for TE may improve earlier recognition of higher risk for TE, better clinical care of these patients and reduce the incidence of TE events. Future prospective, multicenter studies are needed on neurological complications of NS in childhood. Research programs focusing on identifying clinical or laboratory biomarkers of increased risk for neurological manifestations or the efficacy of preventive treatment strategies, in order to prevent these events, could improve quality of care in NS pediatric patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.02.007.

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