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Risks of severe hyponatremia in children receiving hypotonic fluids

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Abstract:	Intravenous fluids are frequently used in hospitalized children. Hypotonic fluids have been the standard of care in pediatrics for many years. This might be explained by the empiricism of early recommendations favoring fluids with dextrose, but insufficient amount of sodium. The risk of hyponatremia (<135 mmol/L) might be increased by the occurrence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in the course of common acute diseases (e.g., bronchiolitis, acute gastro-enteritis, encephalitis, meningitis, etc.) in children. Severe hyponatremia (<130 mmol/L) is often associated with neurologic complications leading to sequelae or even death. Over the last years, hyponatremia-induced by hypotonic fluids has been increasingly reported, significant progress has been made in the understanding of cerebral edema and osmotic demyelination, and several randomized clinical trials have shown weak, but significant evidence that isotonic fluids were superior to hypotonic ones to prevent hyponatremia. However, clinical practices have not much changed in France, as suggested by the analysis of intravenous fluids ordered to the Assistance Publique - Hôpitaux de Paris (AP-HP) central pharmacy (PCH), in 2017. Thus, it would be advisable that national guidelines would be released under the French Health Authorities regarding the safe infusion of infants and children. (198 words).

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Risks of severe hyponatremia in children receiving hypotonic fluids

Key-words: children, hypotonic fluids, SIADH, cerebral edema, osmotic demyelination

Risques d'hyponatrémie sévère chez les enfants perfusés avec des solutés hypotoniques

Mots-clés : enfant, solutés hypotoniques, SIADH, œdème cérébral, démyélination osmotique

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Les auteurs déclarent n'avoir aucun conflit d'intérêt concernant cet article.

Une conférence d'experts devrait être organisée en 2021 par le Service d'évaluation des bonnes pratiques professionnelles de la Haute Autorité de Santé avec la participation des Sociétés savantes suivantes :

- Société Française de Pédiatrie, Groupe Francophone de Réanimation et d'Urgences Pédiatriques
- Société Française de Médecine d'Urgence (SFMU)
- Société de Réanimation de Langue Française (SRLF)
- Société Française d'Anesthésie-Réanimation (SFAR)
- Association des Anesthésistes Réanimateurs Pédiatriques Français (ADARPEF)

Abstract :

Intravenous fluids are frequently used in hospitalized children. Hypotonic fluids have been the standard of care in pediatrics for many years. This might be explained by the empiricism of early recommendations favoring fluids with dextrose, but insufficient amount of sodium. The risk of hyponatremia (<135 mmol/L) might be increased by the occurrence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in the course of common acute diseases (e.g., bronchiolitis, acute gastro-enteritis, encephalitis, meningitis, etc.) in children. Severe hyponatremia (<130 mmol/L) is often associated with neurologic complications leading to sequelae or even death. Over the last years, hyponatremia-induced by hypotonic fluids has been increasingly reported, significant progress has been made in the understanding of cerebral edema and osmotic demyelination, and several randomized clinical trials have shown weak, but significant evidence that isotonic fluids were superior to hypotonic ones to prevent hyponatremia. However, clinical practices have not much changed in France, as suggested by the analysis of intravenous fluids ordered to the Assistance Publique - Hôpitaux de Paris (AP-HP) central pharmacy (PCH), in 2017. Thus, it would be advisable that national guidelines would be released under the French Health Authorities regarding the safe infusion of infants and children. (198 words).

Résumé :

Les solutés de perfusion sont fréquemment utilisés chez les enfants hospitalisés. L'administration de solutés hypotoniques par voie intraveineuse a longtemps constitué la référence en pédiatrie. Cela peut s'expliquer par l'empirisme des recommandations initiales qui ont prôné l'utilisation préférentielle de solutés glucosés, mais hypotoniques du fait d'un contenu insuffisant en sodium. Le risque d'hyponatrémie (<135 mmol/L) peut être accru par la survenue d'un syndrome de sécrétion inappropriée d'hormone antidiurétique (SIADH) au cours de pathologies aiguës (p. ex. bronchiolite, gastro-entérite, encéphalite, méningite, etc.) chez les enfants. L'hyponatrémie sévère (<130 mmol/L) expose à de graves complications neurologiques, responsables parfois de lourdes séquelles ou du décès. Au cours des dernières années, le risque d'hyponatrémie lié à l'utilisation de solutés hypotoniques a été dénoncé, des progrès sont intervenus dans la compréhension de l'œdème cérébral et du syndrome de démyélination osmotique, enfin des essais randomisés ont apporté la preuve de la supériorité des solutés isotoniques sur les solutés hypotoniques. Cependant, les pratiques n'ont guère évolué en France, comme en atteste l'analyse des commandes de solutés pour perfusion à l'Assistance Publique-Hôpitaux de Paris en 2017. Aussi, il serait souhaitable que des recommandations françaises soient émises sous l'égide de la Haute Autorité de Santé. (194 mots)

1. Introduction

Maintenance intravenous fluids (IVFs) are used to support acutely ill children. IVFs are required whenever oral fluid administration cannot be sustained, because of acute gastroenteritis, respiratory distress, neurological impairment, perioperative state, and comfort care for terminal acute or chronic illnesses. Both composition and volume of IVFs should maintain body's water and electrolyte homeostasis, and prevent either volume depletion or fluid overload.

Although IVFs are routinely used in many pediatric facilities, clinical practice widely differs between various institutions and even countries. This might be explained by the empiricism of historical recommendations published about 60 years ago, favoring dextrose 5% in water (D5W) with low amounts of sodium (e.g., a quarter (NS/4) or half (NS/2) of normal saline [NS]) [1]. Furthermore, a Syndrome of Inappropriate secretion of Anti-Diuretic Hormone (SIADH) often occurs in several diseases currently seen in children (e.g., acute gastroenteritis, viral bronchiolitis, encephalitis, meningitis, etc. - Table 1), that impairs the excretion of free water and favors the occurrence of hypotonic hyponatremia [2].

In the 2000's, two American pediatric nephrologists reported a series of children with severe hypotonic fluid-induced severe hyponatremia leading to severe neurological sequelae and death [3,4]. However, it took almost ten years for the pediatric community to realize the superiority of isotonic fluids over hypotonic ones to prevent the rare occurrence, but deadly consequences of hyponatremic encephalopathy. Guidelines have been subsequently released both in the UK and US [5-8]. However, no such recommendations have been made so far in France. Thus, the objective of this review is to sensitize all pediatricians, but also emergency physicians, intensivists, surgeons and anesthetists to the critical importance of using as maintenance IVFs

only isotonic fluids in neonates, infants and children under a close clinical (daily weight and urine output) and biological (daily blood ions) monitoring, while an expert consensus conference would be meanwhile organized under French Health Authorities guidance.*

2. Historical recommendations regarding intravenous fluids use in both adults and children were, indeed, rather empiric.

In the early 50's, various metabolic considerations led the authors to recommend the use of hypotonic fluids at rates from 1.5 to 3.5 liters per square meter per day in adult patients with basically normal endocrine-renal homeostatic systems "to cure themselves from disturbances in water and electrolyte metabolism"[9].

For similar historical reasons, recommendations have been to infuse children with hypotonic fluids. This practice has been mostly based on physiologic calculations [1]. Basal caloric expenditure measured by direct calorimetry in sane children was found to be proportional to body weight: 100 kcal/kg between 0 et 10 kg; 1,000 kcal + 50 kcal/kg between 10 and 20 kg; and 1,500 kcal + 20 kcal/kg above 20 kg of body weight. Water requirements were estimated on the basis of 1ml per kcal, i.e., 1,500 ml/m^2 body surface area (BSA). This pragmatic rule of « 100-50-20 » ml/kg per day is still universally recommended for pediatric infusion. Lastly, the intake of electrolytes provided per 100 calories of various regimens was estimated to reflect both human and cow's milk, i.e., Na+ 3.0 mmol, and K+ 2.0 mmol per 100 kcal per day.

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In 1963, the Assistance Publique - Hôpitaux de Paris (AP-HP) Central Pharmacy (PCH) was asked to manufacture a ready-to-use fluid, initially named « *Lestradet solute* » then later referenced as « *B27* » solute. Besides Ringer-Lactate (RL or *B21*), D5W RL (*B66*), and normal saline (NS or NaCl 9‰), other ready-to-use fluids, either containing more dextrose (D10W or *B45*) or being richer in sodium chloride (*B46, B26*) have been made available to match the specific needs of clinicians (Table 2). However, manufacturing costs and growing availability of commercial fluids have stepwise reduced the PCH offer, such a way that French Pediatric Anesthesiologists recommended again "home-made" fluids to replace the missing D5W RL [10], when their German colleagues benefited from industrial solutions [11].

Over the years, those ready-to-use hypotonic fluids have been largely prescribed in the French children's hospitals, although the important concepts of tonicity and osmolality have been almost forgotten by clinicians. The term '*tonicity*' describes the effect of plasma on cells – hypotonicity makes cells swell and hypertonicity them shrink [12]. The term '*osmolality*' is the result of all osmoles (glucose, ions, lactate, acetate, etc.) added to 1 L of water. Blood osmolality (mOsm/kg) may be estimated by the following formula = [1.86 x Na (mmol/L) + BUN (mmol/L) + glucose (mmol/L)] + 9 (normal range: 275-300 mOsm/L). On the one hand, intravenous infusion of hypo-osmolar fluids (<280 mOsm/L) leads to intravascular hemolysis. On the other hand, intravenous infusion of hyper-osmolar fluids (>600 mOsm/L) damages the vascular endothelium, and facilitates extravascular diffusion. Although dextrose contributes to the initial osmolality of infused fluids, its rapid cellular metabolism ultimately leads to provide excess *free-water* to the body.

3. A growing number of pediatric cases with hypotonic fluid-induced hyponatremia, complicated by catastrophic neurological events.

In 2003, Moritz and Ayus reported more than 50 published cases of serious neurological complications including 26 deaths linked to hospital-acquired hyponatremia resulting from hypotonic fluids [3]. Therefore, they recommended the preferential use of isotonic fluids such as normal saline in children. The main factor contributing to hyponatremic encephalopathy in children was the routine use of hypotonic fluids in patients who had an impaired ability to excrete free-water, as in the postoperative state and central nervous system diseases. In 2005, they reported on 15 prospective studies in over 500 surgical adult and pediatric patients that demonstrate that normal saline effectively prevents postoperative hyponatremia, and hypotonic fluids consistently result in a fall in serum sodium [4].

Furthermore, SIADH was documented in 22/23 (96%) infants in the acute phase of bronchiolitis with normalization of natremia and plasma ADH in the recovery phase [13]. Likewise, high antidiuretic hormone levels and hyponatremia were reported in 52 children with acute gastroenteritis despite being intravenously infused with hypotonic fluids [14]. Bronchiolitis and gastroenteritis are, indeed, frequent acute conditions in infants and young children.

Lastly, large and very large decreases in serum sodium levels, as defined as 8-13, and >13 mmol/L from normal values, respectively, measured during the first month of life in 237 very preterm neonates were significantly associated with impaired functional neurological outcomes at two-year follow-up, after adjustment for gestational age, perinatal and neonatal hospitalization characteristics [15]. The comment about this French single neonatal center study was entitled: « *Hyponatremia in premature infants : not a benign condition* » [16].

4. Prospective randomized clinical trials comparing hypotonic and isotonic fluids in hospitalized children.

In 2006, a first meta-analysis combining 6 studies that compared hypotonic to isotonic maintenance solutions in children showed that hypotonic solutions significantly increased the risk of developing acute hyponatremia (OR 17.22; 95% confidence interval [CI] 8.67 to 34.2), and resulted in greater patient morbidity [17]. Several other randomized clinical trials were subsequently published, including the last one featuring the best methodology (i.e., double-blind assessment) and enrolling by far the highest number (n=690) of pediatric patients [18-20]. Thus, the most recent meta-analyses including more than two thousands pediatric cases showed that overall the relative risk of developing severe hyponatremia (<130 mmol/L) was significantly lower with isotonic IVFs as compared with hypotonic fluids (RR 0.31; 95%CI 0.19-0.50) (Figure 1) [22-24].

The use of isotonic saline is, however, associated with hyperchloremic metabolic acidosis that may favor renal insult [25]. This concern may explain the recent recommendation of using rather « *balanced crystalloids* », such as Ringer-lactate® or Plasma-Lyte® either in the adult Emergency or Critical Care Units [26, 27]. Although the evidence is still weak in acutely ill children, it is wise to recommend the preferential use of isotonic fluids quite similar to plasma composition, such as Plasma-Lyte 148® (Baxter) or Isopedia® (Fresenius-Kabi). The latter formula actually contains a reduced concentration of dextrose 1.1% in water, as compared with current ready-to-use fluids (D5W). Nevertheless, this reduced content normally covers body glucose needs (5 – 6 mg/kg BW per min.) and prevents the rare occurrence of hypoglycemia in young infants, with sometimes very severe neurological sequelae [28-30].

It is not possible to predict the effect of administering intravenous fluids on plasma sodium without considering concurrent urinary losses [31]. Urine is hypotonic if its electrolyte concentration is lower than that of plasma, thus excretion of electrolyte-free water will increase the plasma sodium concentration. Conversely, urine is hypertonic if its electrolyte concentration is higher than that of plasma, thus excretion of hypertonic urine will lower plasma sodium concentration. Hyponatremia occurs whenever ingested or infused water content exceeds impaired urinary free-water excretion (SIADH), or when large free-water losses (e.g., *diabetes insipidus*) or osmotic diuresis (e.g., *diabetes mellitus*) occur. Loss or gain of approximately 3 ml of water per kilogram of body weight will change the plasma sodium concentration by approximately 1 mmol/L. In the absence of urinary loss of water, 1ml of 3% saline per kilogram of body weight will increase plasma sodium concentration by about 1 mmol/L.

5. Prevention and treatment of hyponatremic enkephalopathy.

Pathophysiological mechanisms contributing to hyponatremia, and its potential catastrophic neurological consequences have been reviewed in 2000 [32]. Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain. Partial restoration of brain volumes occurs within a few hours as a result of cellular loss of electrolyte (rapid adaptation). Normalization of blood volume is completed within several days through the loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the brain persists despite the normalization of brain volume. Proper correction of hypotonicity reestablishes normal osmolality without risking damage to the brain. Overly aggressive correction of hyponatremia can lead to irreversible brain damage.

Disorders of plasma sodium, causes, consequences, and correction have been recently reviewed in light of recent experimental findings [33]. Hypotonicity makes cell swell, and hypotonicity them shrink. Solute concentrations must be equal inside and outside the cells because water channels (aquaporins) make cell membranes permeable to water [34]. The « sodium pump » (Na^+/K^+-ATPase) actively extrudes out of the cell 3 sodium ions for 2 potassium ones in order to keep cell membrane potential, whereas aquaporins control water free movement across cell membrane that maintains osmotic equilibrium. Sodium readily crosses systemic capillary membranes through clefts between endothelial cells. As a result, the sodium concentrations of plasma and interstitial fluid are nearly identical, with a small difference created by intravascular albumin [35]. In contrast, brain capillaries have tight endothelial junctions and are lined by astrocytic foot processes, creating a "*blood-brain barrier*" not permeable to sodium [36]. Consequently, an abnormal plasma sodium concentration causes water to enter, or leave brain tissue. Because the brain is confined inside the skull, only a small degree of brain swelling or shrinkage is compatible with life. This is why children whose cerebral compliance is lower might be more susceptible than adults to the disastrous consequences of hypotonic fluids-induced severe hyponatremia. Extreme hypotonicity ruptures cell membranes, damages the cytoskeleton, and causes breaks in the DNA ultimately leading to apoptosis [37]. Over time, however, cells protect their volume and survive by adjusting intracellular solute contents. Organic osmolytes are small intracellular molecules (e.g., glutamate, taurine, and myo-inositol) normally acting as metabolic and counteracting cytoprotectants in high osmolarity and other cellular stresses [38]. Hypotonicity promotes the release of osmolytes from cells through volume-sensitive leak pathways, while osmolyte-accumulating transporters are down-regulated. Conversely, hypertonicity up-regulates taurine and the myo-inositol transporters. These physiological mechanisms allow cells to maintain intracellular solute concentrations that

are equal to the osmolality of hypotonic or hypertonic plasma, with little change in cell volume [39].

Clinical manifestations of hyponatremia are primarily neurologic. The release of glutamate, an excitotoxic mediator, may explain the frequent occurrence of seizures. Rapid changes in plasma sodium in either direction can cause severe, and sometimes lethal brain edema. Brain injury after rapid correction of chronic hyponatremia manifests as a biphasic illness called the osmotic demyelination syndrome, that include seizures, behavioral abnormalities, and movement disorders [40]. The most severely affected patients may become « *locked in* », unable to move, speak, or swallow because of demyelination of central pons.

The optimal management of hypotonic hyponatremia requires balancing the risks of hypotonicity against those of therapy. The presence of symptoms and their severity largely determine the pace of correction. Patients who have symptomatic (i.e., seizures or coma) and severe hyponatremia (<125 mmol/L) with concentrated urine and clinical normal volemia require the rapid infusion of hypertonic (3%) saline (1 ml/kg up to 100ml bolus) in order to raise serum sodium levels >125 mmol/L and rapidly achieve control of clinical seizures [41]. A frequent misconception is to treat severe hypotonic hyponatremia using large volumes of normal saline, as hyponatremia is further aggravated due to powerful natriuresis that ensued. Otherwise, less severe hyponatremia (>125 mmol/L) should be corrected using fluid restriction at a slower pace of no more than 0.5-1.0 mmol/L per hour [42]. Frequent monitoring of both vital signs and ion blood levels mandates the transfer of the child into a Pediatric Intensive Care Unit.

Acute hyponatremia was shown to be associated with prolonged hospitalization or frequent re-hospitalizations with increased costs [43]. Furthermore, it was shown to be associated with a 30-40% higher risk of mortality 1 year after admission [44]. However, in this large Danish national database, no clear increase in mortality was observed with more severe hyponatremia (<130 mmol/L). This paradoxical finding might be explained by both the various etiologies observed in a large database and whether hyponatremia condition has occurred acutely or chronically.

6. Conclusion : towards French guidelines in maintenance intravenous fluids

In 2013, the Canadian Society of Paediatrics published a warning about the risks of hyponatremia in acutely ill children infused with hypotonic fluids, and strongly recommended the use of isotonic fluids such as D5W with normal saline [45].

In the United Kingdom, guidelines have been released by the '*National Institute for Health and Clinical Excellence*' (NICE) both in adults in 2013 and children in 2015 [5, 6].

On the same year, a review article made strong recommendations in favor of isotonic fluids for maintenance intravenous fluids in acutely ill patients (Fig. 2) [7]. Recently, the Subcommittee on Fluid and Electrolyte Therapy of the American Academy of Pediatrics published clinical practice guidelines on maintenance intravenous fluids in children [8]. Meanwhile, warnings and signal assessment reports on the risks of hypotonic fluids-induced hyponatremia were released both by the European Medical Agency (EMA) on 31st March 2017, and the French National Safety Medicine Agency (ANSM) on June 2017 [46, 47].

As about one third of the patients managed in AP-HP hospitals were apparently still infused with hypotonic IVFs, as suggested by pharmacy orders to the '*Agence Générale des Équipements et des Produits de Santé'* (AGEPS) in 2017, as follows: i) Normal Saline 1,897,000 liters (56%) and Ringer-lactate® 362,000 liters (10%); ii) 'Polyionic fluids' 468,000 liters (14%) and D5W 673,000 liters (20%), it is hoped that French guidelines would be soon released by concerned National Societies and endorsed by French Health Authorities, in order to prevent the rare but potentially catastrophic neurological complications of unrecognized hypotonic hyponatremia in acutely ill patients on maintenance IVFs [48].

(Main text 10 pages, 27 paragraphs, 229 lines, 2,502 words, 17,309 characters including spaces.)

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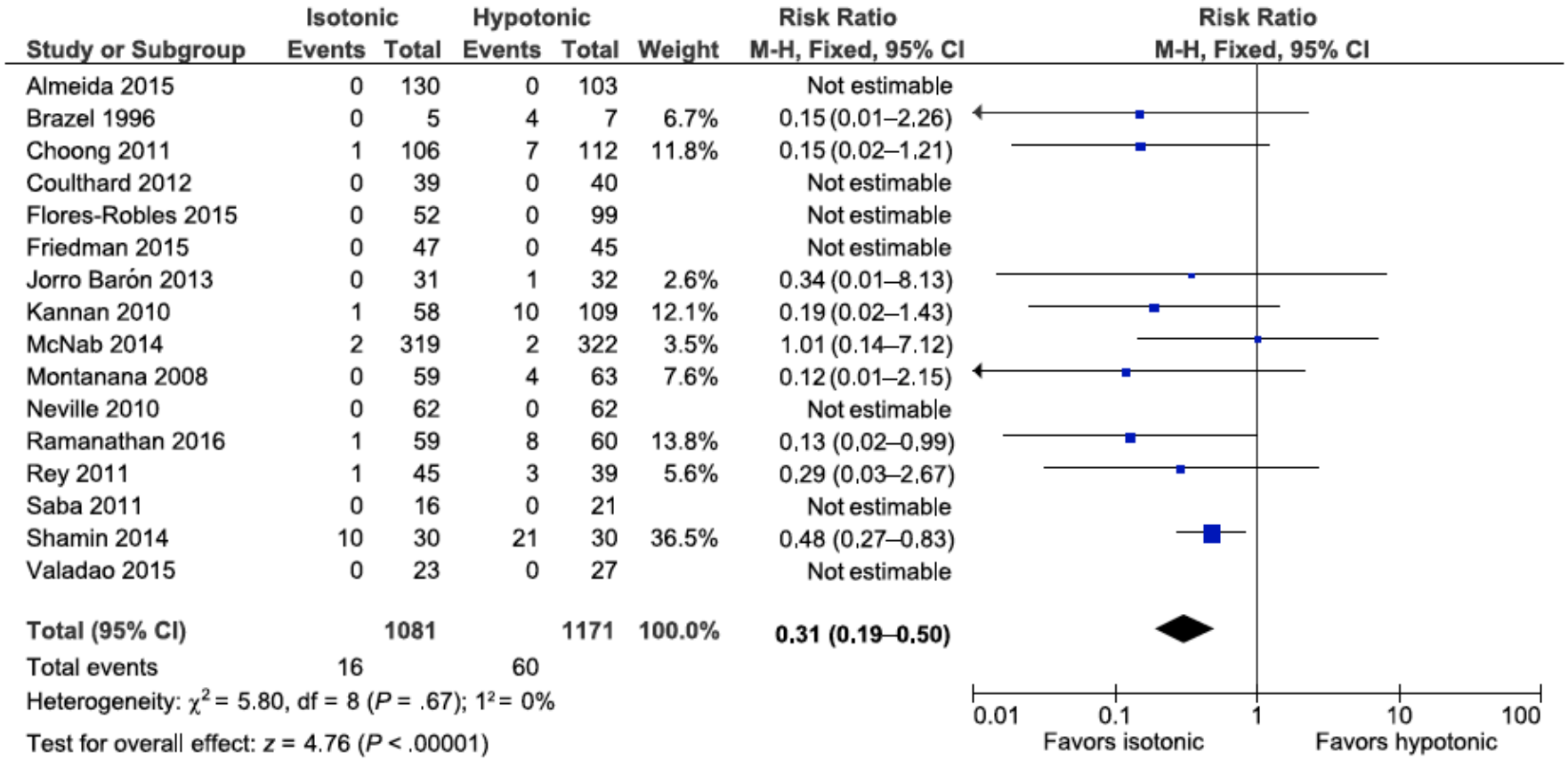
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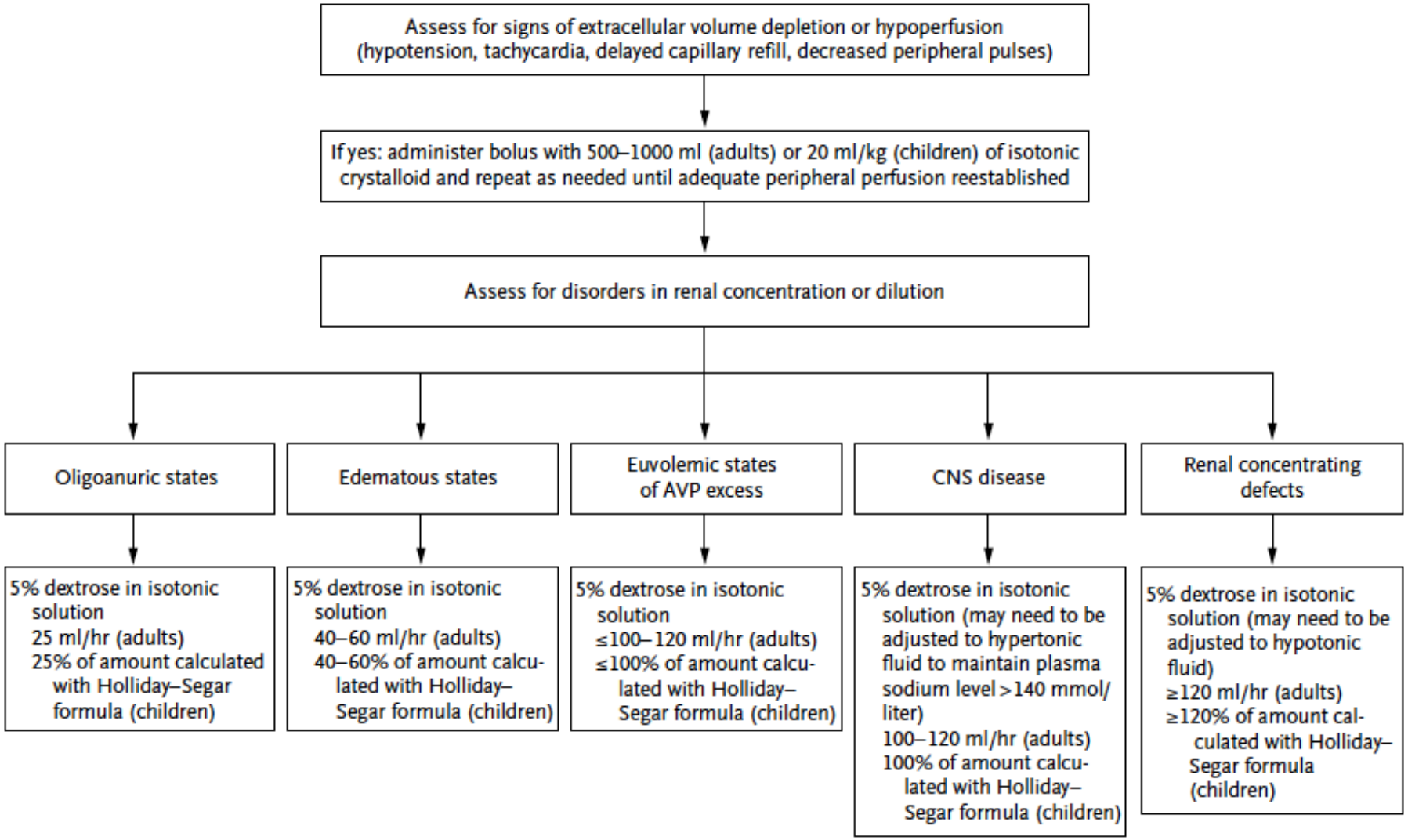
Fig. 1 – Forest plot of RCTs comparing isotonic and hypotonic fluids in children with the outcome of severe hyponatremia (<130 mmol/L)



Using a random model and Mantel-Haenzel statistics, df=degrees of freedom

Source : *Pediatrics* 2018 ; 142(6):e20183083. Supplemental Figure 4.
(Authorization pending)

Figure 2 – Guide to maintenance intravenous fluid therapy in acutely ill patients.



Since most hospitalized patients are at risk of hyponatremia from AVP excess, in most acutely ill adults, the safest type of maintenance solution and rate of administration are 5% dextrose in a solution of 0.9% saline at a rate of 100 to 120 ml per hour. In children, the equivalent dose is either 1500 ml per 1.73 m^2 of body-surface area or an amount calculated with the use the Holliday-Segar formula (100 ml per kilogram per 24 hours for the first 10 kg of body weight, plus 50 ml per kilogram per 24 hours for weight greater than 10 to 20 kg, and an additional 20 ml per kilogram per 24 hours for weight above 20 kg).

The rate and composition of fluids will need to be adjusted for certain conditions.

- Patients at risk for fluid overload require fluid restriction.
- Patients with clinically significant concentrating defects require an increased volume of hypotonic fluids to keep up with ongoing urinary free-water losses.
- Hypotonic fluids should be administered only if there is a specific indication, and they should be avoided if hyponatremia is present.
- In patients with central nervous system (CNS) diseases who are at risk for cerebral edema, the plasma sodium concentration should be maintained at greater than 140 mmol per liter to prevent cytotoxic cerebral edema.

Source : Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely ill patients. *N Engl J Med* 2015 ;373(14) :1350-60.
(Autorized by the N. Engl J Med)

Table 1. Conditions requiring special considerations in maintenance fluid therapy

Free-water restriction for euvolemic states of AVP excess

- CNS disturbances
  - Meningitis
  - Encephalitis
  - Brain tumors
  - Head injury
  - Cerebritis
  - Subarachnoid hemorrhage
- Pulmonary diseases
  - Pneumonia
  - Asthma
  - Bronchiolitis
  - Tuberculosis
- Cancer
- Postoperative state

Fluid restriction for edematous states

- Congestive heart failure
- Nephrosis
- Cirrhosis

Fluid and sodium restriction for oliguric states

- Acute glomeronephritis
- Acute tubular necrosis
- End-stage renal disease

Increased free-water requirements for renal concentrating effects

- Congenital nephrogenic diabetes insipidus
- Sickle Cell Disease
- Obstructive uropathy
- Reflux nephropathy
- Renal dysplasia
- Nephronophtisis
- Tubulointerstitial nephritis
- Use of lithium

Increased sodium and water requirements for solute diuresis

- Diuretic phase of acute tubular necrosis
- Postobstructive diuresis
- Immediate postoperative renal transplantation
- Diabetic ketoacidosis
- Bartter's syndrome
- Fanconi's syndrome
- Cerebral salt wasting
- Adrenal insufficiency

Increased free-water requirements for extrarenal free-water losses

- Burns
- Prematurity in neonates
- Fever
- Acute gastroenteritis

Source : Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely ill patients. *N Engl J Med* 2015 ;373(14) :1350-60. (Autorized by the N Engl J Med)

Table 2 – Commercially available fluids for intravenous infusion in children in France.

	Available in AP-HP Hospitals			Content for 1,000 mL							
PCH Reference	Pharmaceutical Company	Fluid name	Fluid code	Dextrose	NaCl	KCl	$CaCl_2$	Ca^{+2} gluconate	Na^+ lactate	$MgCl_2$	Water As needed for
B21	Baxter	RINGER LACTATE BAX VIAFLO	500 mL: 10139351 1000 mL: 10139331	-	6 g	0.4 g	0.27 g	-	3.2 g	-	1000 mL
B25	Baxter	POLYIONIQUE 2AG10 BAX	500 mL: 10366132	110 g	4 g	2 g	-	-	-	-	1000 mL
B26	Baxter	POLYIONIQUE 1AG5 BAX	500 mL: 10139357 1000 mL: 10139345	55 g	4 g	2 g	-	-	-	-	1000 mL
B27	Chais du Marais	Dextrion G5 FV	250 mL: 10073763 500 mL: 10073765	55 g	2 g	1.5 g	-	1 g	-	-	1000 mL
B45	BBraun	COMPENSAL 15 G10 SOL INJ FV	250 mL: 10241898 500 mL: 10241897	110 g	2 g	1.5 g	-	1 g	-	0.5 g	1000 mL
Plasmalyte 148	Baxter	Plasmalyte Viaflo®	500 mL	-	5.26g	0.37g		5.02g	3.68g acetate	0.3g	1000 mL
ISOPEDIA	Fresenius	Isopedia®	100 mL 250 mL 500 mL	11g	6.4g	0.298g	0.147g		4.02g acetate	0.2g	1000 mL

Source : Pharmacie Centrale des Hôpitaux (PCH) - Agence Générale des Équipements et Produits de Santé (AGEPS), Assistance Publique – Hôpitaux de Paris (AP-HP).

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Mme le Pr. Brigitte Chabrol
Editor-in-Chief
Archives de Pédiatrie

Paris, le 4 juin 2020

Ref. ARCPED-D-20-00023
Title : Risks of severe hyponatremia in children receiving hypotonic fluids

Chère Brigitte,

En premier lieu, nous souhaitons remercier chaleureusement l'Éditeur-en-Chef des *Archives de Pédiatrie* d'accepter la publication, sous réserve de modifications, de cette revue de la littérature qui souhaite attirer l'attention de la communauté pédiatrique sur les risques potentiels d'une hyponatrémie sévère, avec parfois des conséquences neurologiques catastrophiques, chez les enfants perfusés avec des solutés hypotoniques comme ceci est encore trop souvent le cas en France.

Malheureusement, mon projet d'organiser une conférence d'experts sur les solutés perfusés, avec le soutien de l'HAS en 2020, n'a pu aboutir du fait de la pandémie à COVID-19. Espérons que ce ne soit que partie remise en 2021…

Nous souhaitons également remercier nos deux relecteurs pour leurs remarques judicieuses et bien fondées. Nous espérons que les modifications apportées (surlignées en jaune dans cette version révisée) répondent bien à leurs questions.

<u>Relecteur n°1</u> :

- *Certains paragraphes sont très longs et susceptibles d'être raccourcis (3 pages pour le 2 Historique des recommandations ou encore plus de 3 pages pour le 5 Prévention)*
    - Le **chapitre n°2 a été sensiblement raccourci** (2 vs. 3 pages), notamment en ce qui concerne les recommandations chez l'adulte publiées dans *le N Engl J Med* 1954. Par contre, le rationnel physiologique sur lequel reposent encore les recommandations actuelles chez l'enfant a été conservé, de même que les deux paragraphes donnant la composition des solutés de perfusion disponibles et encore largement utilisés en France (Table 2) ainsi que celui décrivant les concepts physiologiques fondamentaux d'*osmolalité* et de *tonicité*.

    - Le **chapitre n°5 Prevention and treatment of hyponatremic encephalopathy a été également simplifié et raccourci** (2,3 vs. 3 pages). Mais, les données expérimentales rapportées sont fondamentales pour comprendre les conséquences neurologiques potentiellement réversibles (anomalies de la

transmission synaptique, accumulation d'osmolytes cytoprotecteurs) ou au contraire irréversibles (démyélination, apoptose neuronale). En outre, il décrit les manifestations neurologiques de l'hyponatrémie sévère et leur traitement par l'injection de soluté hypertonique salé à 3%, à la différence du sérum physiologique à 9‰.

- Enfin, le **chapitre 6 Incidence of severe hyponatremia in French hospitals** a été intégré [moyennant la suppression des données de l'enquête sur les hyponatrémies à l'Hôpital Louis Mourier] dans le paragraphe 7 **Conclusion : towards the release of French guidelines in intravenous fluids** afin de justifier l'élaboration de recommandations consensuelles Françaises, après celles émises au Canada, en Angleterre et aux USA.

- Ainsi le texte de l'article révisé a été globalement raccourci de plus de 20%.

- « *En règle générale, la description de la littérature ne s'appuie que sur des résultats chiffrés (OR ou RR 95%CI des méta-analyses par exemple) ».*
  - La description de la littérature concernant les études randomisées contrôlées s'appuie sur trois méta-analyses, la première publiée en 2006 et les 2 autres publiées par la *Cochrane 2014* et dans le *JAMA 2015* qui a été reprise dans les recommandations de l'American Academy of Pediatrics en 2018 en donnant maintenant les **OR/RR [95%CI]** pour le risque d'hyponatrémie sévère (<130 mmol/L) entre solutés isotoniques et hypotoniques (Table 2).

- *« Il existe de très nombreuses abréviations non expliquées (D5W, NS/2, D2,5W ???) ».*
  - Nous comprenons cette remarque sur les nombreuses abréviations qui figurent dans le texte, mais d'une part elles ont été **toutes définies lors de leur première apparition dans le texte**, d'autre part ces **abréviations sont bien connues des pédiatres, urgentistes ou réanimateurs Anglo-Saxons** (p.ex. Dextrose 5% in Water = D5W, c'est l'équivalent de notre G5% ; D10W = G10% ; Normal Saline = NS, soit notre « sérum physio. » à 9‰ qui n'est d'ailleurs pas si « *physiologique* », d'où l'utilisation croissante de solutés de perfusion dit équilibrés (« *balanced crystalloids* »). Depuis que la langue officielle des Archives de Pédiatrie est devenue l'anglais, force est d'utiliser les sigles anglo-saxons communément utilisés et acceptés…

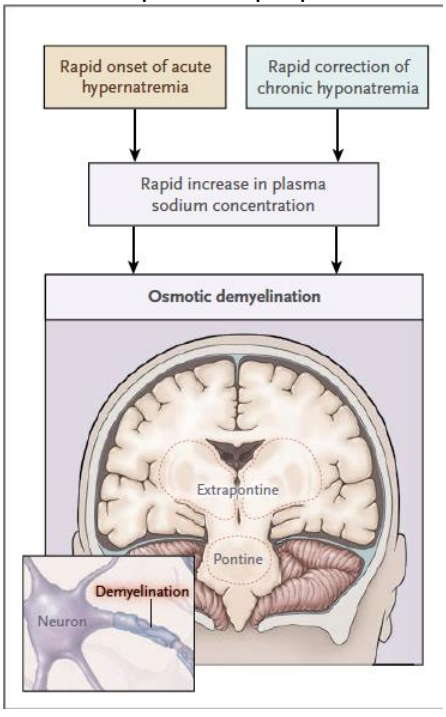
- *« La figure 2 mériterait d'être plus détaillée car elle apporte des informations très utiles et claires, mais pas d'information sur sa provenance ? »*
  - La source de la Figure 2 était donnée en p.24/27 du manuscrit original (N Engl J Med 2015 ;373(14) :1350-60.

<u>Relecteur n°2</u> :

- « *Comme le rappellent les auteurs dans un chapitre (qu'il faut raccourcir**, ce qui a été fait**), ce risque d'hyponatrémie et leurs conséquences neurologiques est connu depuis longtemps, mais on note encore trop souvent l'emploi de ce type de solutés* ».
  - C'est précisément l'objet de cette revue de la littérature que de sensibiliser à nouveau les prescripteurs en pédiatrie aux risques d'hyponatrémie sévère chez les

enfants perfusés par des solutés hypotoniques qui apportent de l'eau libre, quand son élimination est diminuée notamment du fait d'un syndrome de sécrétion inappropriée d'hormone antidiurétique, particulièrement fréquent en cas de pathologie virale aiguë comme une bronchiolite, une gastro-entérite, etc. (cf. les dernières lignes de l'introduction)

- « *Cependant, il aurait été intéressant de mieux décrire les lésions de myelinolyse pontine visible en IRM, l'article du Lancet date de 1986, où l'emploi de l'IRM n'était pas aussi large que maintenant, une iconographie aurait été intéressante.* »
    - La seule référence qui date de 1986 est la n°44 : Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 1986 ;314 :1535-42. Cet article rapporte 8 patients adultes présentant à l'admission une hyponatrémie <115 mmol/L et dont l'état neurologique s'est dégradé dès que la correction de l'hyponatrémie était rapide >12 mmol/L/24h. L'article comporte bien une image de scanner cérébral mais pas d'IRM et une macrophotographie du pont cérébral à l'autopsie d'un des patients.
    - Cette référence a donc été remplacée par une référence plus récente décrivant le pronostic neurologique de 31 patients adultes (+31 alcooliques) ayant une hyponatrémie sévère traités dans 46 services de réanimation français avec un bon pronostic à un an dans 50% des cas.
    - Si le relecteur souhaitait qu'une iconographie intéressante figure dans notre revue, on pourrait proposer les images suivantes :



N Engl J Med 2015 ;372 :55-65

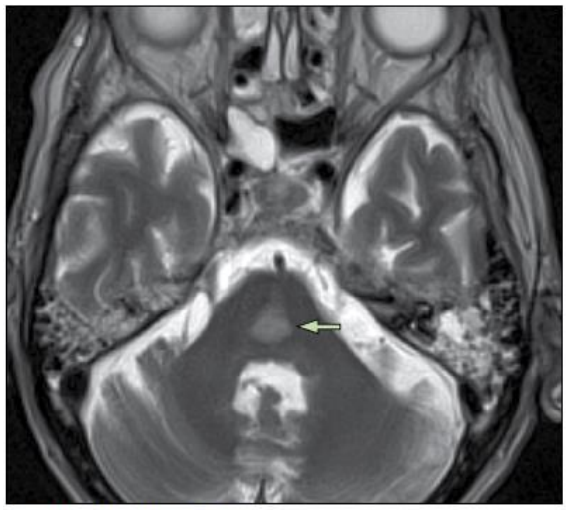


Figure: An MRI scan of central pontine myelinolysis
T2-weighted fluid-attenuated inversion recovery brain MRI shows a triangular area of increased signal intensity in the pons (green arrow) consistent with central pontine myelinolysis.

Lancet 2018 ;392 :2213

- *« Il serait important de rappeler la possible récupération ad integrum de ces lésions si l'enfant est pris en charge rapidement et correctement ».*
    - P. 11, l.241-52: The optimal management of hypotonic hyponatremia requires balancing the risks of hypotonicity against those of therapy. The presence of symptoms and their severity largely determine the pace of correction. Patients who have symptomatic (i.e., seizures or coma) and severe hyponatremia (<125

mmol/L) with concentrated urine and clinical normal volemia require the rapid infusion of hypertonic (3%) saline (1 ml/kg up to 100ml bolus) in order to raise serum sodium levels >125 mmol/L and rapidly achieve control of clinical seizures [41]. A frequent misconception is to treat severe hypotonic hyponatremia using large volumes of normal saline, as hyponatremia is further aggravated due to powerful natriuresis that ensued. Otherwise, less severe hyponatremia (>125 mmol/L) should be corrected using fluid restriction at a slower pace of no more than 0.5-1.0 mmol/L per hour [42]. Frequent monitoring of both vital signs and ion blood levels mandates, therefore, the transfer of the child into a Pediatric Intensive Care Unit.

- Si une correction *rapide* de l'hyponatrémie sévère par un bolus iv de sérum salé hypertonique (3%) permet souvent de faire cesser les convulsions cliniques en remontant la natrémie vers 125 mmol/L, la correction de l'hyponatrémie hypotonique doit être autrement *lente* de sorte à corriger la natrémie d'environ 0,5 mmol/L et par heure et de permettre une adaptation métabolique encéphalique progressive afin d'éviter la survenue de séquelles neurologiques.

- On ne peut qu'être d'accord avec notre relecteur sur le fait qu'une prise en charge correcte permette d'espérer une récupération *ad integrum* des lésions neurologiques. Néanmoins, la mortalité et la morbidité significatives des hyponatrémies hypotoniques sévères justifient tous les efforts de prévention en substituant les solutés isotoniques aux solutés hypotoniques traditionnellement utilisés chez l'enfant en France.

Espérant avoir répondu d'une façon satisfaisante à toutes les questions de nos relecteurs que nous remercions encore, je te prie de croire, Chère Brigitte, en mes sentiments les meilleurs.



Jean-Christophe Mercier