HYDROELECTROLYTIC IMBALANCE IN MENTAL RETARDATION AND AUTISM SPECTRUM DISORDERS

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Abstract: Autismul (ASD), ca si retardul mental (MR) cu care se asociaza adeseori, au in comun deficitul de comunicare sau comunicarea inadecvata. O consecinta a acesteia este hidratarea insuficienta, cu efect in accentuarea dezechilibrului hidro-electrolitic corelat de altfel si cu medicatia anticonvulsivanta administrata. Determinarea parametrilor biochimici implicati in realizarea echilibrului hidric si electrolitic (ioni, lactat, osmolaritate, raport uree:creatinina) s-a realizat pe un lot compus din 62 de pacienţi cu diagnostice de MR şi ASD. Au fost constatate 41 de acidoze metabolice prin supraîncărcare cu acizi si 51 de perturbări ale echilibrului hidroelectrolitic, raportul uree : creatinină fiind crescut la 57 subiecţi. Frecvenţa mare a cazurilor cu modificari ale echilibrului hidric justifică studiul aspectelor genetice legate de hormonul antidiuretic şi/sau de receptorii acestuia.

Abstract: Autism spectrum disorders (ASD) and often associated mental retardation (MR) are linked by communication deficits or inadequacies. One of the consequences of such disorders is insufficient hydration, which acts to accentuate the hydroelectrolytic imbalance already correlated to prescripted anticonvulsive medication. This study aimed to determine biochemical parameters linked to hydric and electrolytic balances (ions, lactate, osmolarity, bun:creatinine ratio) using a study group of 62 MR and ASD patients. Results revealed 41 cases of metabolic acidosis by acid overload, 51 hydroelectrolytic imbalances and elevated bun:creatinine ratio in 57 patients. Such high occurrences of hydric balance disorders justify further genetic studies on the antidiuretic hormone and/or its receptors.

INTRODUCTION

Poor communication influences interpersonal relationships and slowly leads to isolation and a narrowing of activity prospects. Such conditions may eventually evolve to serious pathology. Communication contraction may occur during childhood, because of the child’s inability to acquire the specifics of verbal and non-verbal communication, or in late life, as mental or motor handicaps set in. The former case is characteristic of severe mental retardation (MR) and is one of the three defining aspects of autism spectrum disorders (ASD), together with diminished social interaction and the constant performance of restrictive, repeated and stereotypical activities. ASD occur together with severe MR in 75% of cases (Filipek et al, 1999) and no cause-effect relationship could be established between the two diagnoses so far. In order to determine criteria for the early diagnosis of autism (aiming for under 3 years of age), a great number of studies was carried out, but few focused on revealing the differences between ASD and MR. According to Osterling et al, (2002), based on a retrospective study of video recordings of children’s behavior during the first years of life, signs that differentiate autism from MR are evident from as early as one year of age. However, it must be pointed out that in such situations, diagnosis is deeply subjective and strongly dependant on the proficiency of the diagnostician. In the search for objective methods to evaluate a diagnosis, the present study proposes comparing hydroelectrolytic balance data for MR and ASD, supposing an analogy with elderly patients which exhibit frequent dehydration as a consequence of losses of movement autonomy or cognitive functions which limit access to fluids (Ferry M., 2005), a situation also commonly encountered in mental and physical handicap.

MATERIALS AND METHODS

After obtaining informed consent from parents and legal guardians, a study lot of 62 patients (19 girls and 43 boys) was formed. Out of these patients, 32 were under 18 and 30 were adults under 22. The patients, all under neuropsychiatric supervision in Galati with diagnoses of ASD and MR, were in their majority institutionalized (46/62), while the rest (mostly ASD sufferers) were in family care. The study lot was divided into three categories, according to respective diagnosis: ASD (8 patients), ASD+MR (15 patients) and MR (39 patients). Mental retardation was severe (¾ of cases) and moderate.

Over two thirds of subjects received antipsychotic neuroleptic medication (risperidone/Torendo, Rispen, aliphatic side chain phenothiazine/Levomepromazin, Plegomazin, butirophenone/ Haloperidol), antispastics (Orfiril, carboxiamide derivatives/Carbamazepine, sodium valproate/Depakine and Taver, benzodiazepine derivatives/Rivotril,

lamotrigine/Lamictal, barbiturates/Fenobarbital) and anxiolitic medication (diazepam, nitrazepam, bromazepam/Calmepam, Meprobamat). Medication was assigned for occurrences of hyperkinezia, mania and hetero- or auto-aggression, leading up to automutilation.
Patients gave two blood samples (serum and heparin plasma) to permit measurements on ion concentrations for sodium, potassium, chlorine, calcium, magnesium, bicarbonate, phosphate as well as urea, creatinine and lactate levels. All tests were performed using MicroSlides techniques, on the Vitros 950 dry biochemistry automated analyzer (Ortho Clinical Diagnostics, Johnson & Johnson). Based on the measurements, osmolarity and bun:creatinine ratios were calculated and the hydric balance was interpreted according to reference intervals for biological values given in literature (Schäffler A. et al, 1995; Wallach J., 2000). Estimations were made to a confidence interval of 95%. The study was carried out within the "Sf. Ioan" Children's Clinical Emergency Hospital in Galaţi.

RESULTS AND DISCUSSIONS

Blood sample results revealed frequent anomalies in electrolytic ion levels, as listed below:

- elevated sodium levels (above 145 mmol/L) in 37 patients: 23/MR, 10/MR+ASD and 4/ASD;
- elevated potassium levels (above 5 mmol/L) in 10 patients: 6/MR, 3/MR+ASD and 1/ASD;
- elevated chlorine levels (above 108 mmol/L) in 3 ASD patients;
- diminished ionic calcium levels, as calculated from the McLean-Hastings nomogram, (below 1.18 mmol/L) in all patients: 39/MR, 15/MR+ASD and 8/ASD;
- elevated phosphate levels (above age requirements) in 18 patients: 10/MR, 4/MR+ASD and 4/ASD;
- elevated magnesium levels (> 0.94 mmol/L) in 4 patients: 1/MR, 2/MR+ASD and 1/ASD;
- diminished bicarbonate levels (below age requirements) in 1 ASD patient.

Considering the large number of ion level deviations, mostly concerning sodium ions, osmolarity and ion gaps were calculated in order to evaluate clinically relevant homeostatic disorders.
Anion gaps (AGap) were calculated using formula (1):

$$AGap = [Na^+] - ([ECO_2] + [Cl^-]) \quad (1)$$

which was deduced from the general formula (2):

$$AGap = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [HCO_3^-] + [proteins]) \quad (2)$$

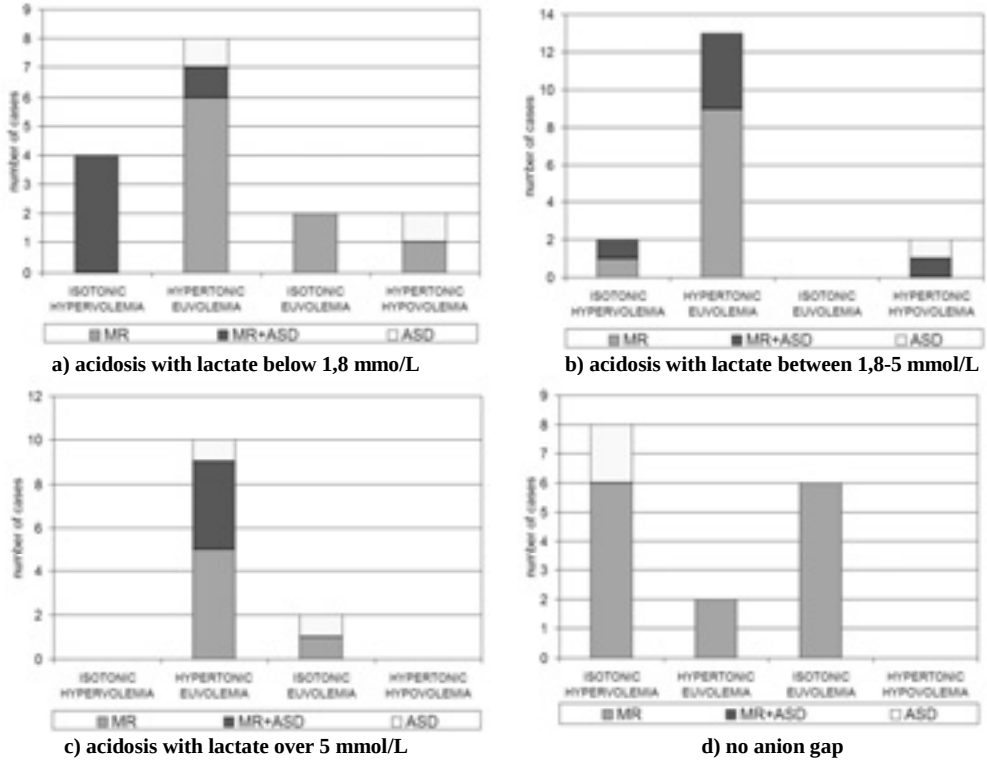
by admitting that negative protein charges cancel out positive potassium, calcium and magnesium ion charges. The anion gap is an electrolytic balance validation criterion, a value of over 15 mmol/L indicating acidosis, while levels below 1 mmol/L indicate alkalosis. Both acidosis and alkalosis may have metabolic or respiratory origins (Despopoulos and Sillbernagl, 2003). Anion gap calculations revealed 41 acidoses: 24 in the MR group, 12 in MR+ASD and 5 in ASD patients. A significant (but not exclusive) contribution to the anion gap is the concentration of sodium ions, with a correlation coefficient of 0.71, $p < 0.001$ for Na^+ - *Anion gap* dependencies, when alkaline reserves are available and chlorine concentrations are within normal limits. Therefore, sodium levels may be used to indirectly diagnose metabolic acidosis by acid overload.

Lactate dosing revealed high lactate levels in 31 patients, as follows: in 20 patients (11/MR, 5/MR+ASD, 2/ASD) lactate was between 1.8 – 5 mmol/L, while in 13 patients (7/MR, 4/MR+ASD, 2/ASD) lactate was over 5 mmol/L and up to 10 mmol/L. As a result, 27 of the 41 diagnosed cases correspond to acidosis due to lactic acid overload, while the 12 cases in which lactate levels were above 5 mmol/L are listed as severe lactic acidosis. Such electrolytic imbalances must be interpreted considering the default aqueous environment, and therefore the osmolarity was calculated according to formula (3):

$$CO\ (mOsm/kg) = 2[Na^{+}](mmol/L) + [Glucose]\ (mg/dL)\ /\ 18 + [Urea](mg/dL) / 2.8 \quad (3)$$

(CO = calculated osmolarity)

By referring to standard intervals (275-295 mOsm/kg), 4 cases of elevated osmolarity (1/MR, 1/MR+ASD and 2/ASD), 14 cases of low osmolarity (7/MR, 4/MR+ASD and 3/ASD) as well as 44 normal osmolarities were found. However, normal osmolarity levels were coupled with increased sodium levels in 37 cases. Out of the total 62 patients, only 7 presented normal hydroelectric and acido-basic balances, while the rest exhibited different combinations of acidosis and/or volemias. Hydric imbalances recorded in this study are listed in figure 1a-d.



a) acidosis with lactate below 1,8 mmo/L

b) acidosis with lactate between 1,8-5 mmol/L

c) acidosis with lactate over 5 mmol/L

d) no anion gap

Fig.1 Hydroelectrolytic imbalance in subjects with MR and ASD

Since none of the patients received intravenous sodium and excessive alimentary intake is unlikely, it can be concluded that the hypernatremia is partly due to the deficit of fluids, as a result of the patients inability to quench their own thirst (mostly institutionalized individuals) as well as to water losses along the digestive tract (3 patients suffer from digestive diseases such as functional colonopathy and gastroesophageal reflux) or hormonal influenced water losses (in patients who do not fulfill any of the above mentioned criteria) (Rose and Post, 2001).
By analyzing the characteristics of the metabolic acidoses present within the study lot – elevated osmolarity with normal bicarbonate levels, elevated sodium, potassium and chloride levels – by comparison to the specifics of partially compensated metabolic acidosis, described previously (Métais et al, 1980), i.e. an elevated osmolarity with low bicarbonate and sodium and normal potassium and chlorine, it can be concluded that the differences between the two profiles are the water deficits. Under normal hydration, patients' carbon dioxide levels would be diminished, and potassium, sodium and chlorine levels would normalize or drop below references. Correcting the hydric balance would also restore phosphate levels, as well as drastically reduce calcium levels. Adjustments to volemia would not, however, modify the occurrence of acidosis, which is sustained by high phosphate levels, which captures calcium ions and maintains hypocalcemia. (Lederer et al, 2007). The three osmoregulatory systems are: thirst, antidiuretic hormone (ADH, arginine-vasopressin) and renal diuresis. When suspecting a disorder in the renal regulation of the hydric balance the common approach is to perform tests for: bun:cratinine ratios - above 20 coupled with elevated osmolarity or sodium (Eaton et al, 1994; Gross et al, 1992; Simel et al, 2008) – as well as urinary osmolarity and the subsequent ratio between this and plasmatic osmolarity (Leibovitz A., 2007). The investigation of renal function by completely analyzing urine over 24 hours, while necessary, was difficult, considering the main diagnoses to be dealt with. Bun:creatinine levels were significantly increased in 57 cases (37/MR, 12/MR+ASD, 8/ASD). The bun:creatinine ratio may dissociate diagnoses in cases of deficient renal function. A high ratio signals a superior increase in urea concentrations over creatinine, usually as a cause of dehydration, while a normal ratio signifies proportional increases for the two analytes, often pathologically associated with kidney dysfunction or urinary tract obstructions. The accentuated increase of the bun:creatinine ratio encountered in most patients is another convincing argument to support the association between dehydration and intellectual development disorders.
Considering the situation, it can be concluded that for the MR and ASD patients included in this study cannot simply rehydrate as a consequence of thirst. As described previously by Macdonald et al, 1989, within psychiatric institutions, hypersodic dehydration is mostly due to environmental conditions. Mentally disabled children and adults are incapable of expressing thirst or reaching water, as are elderly patients who exhibit diminished osmotic regulation (through as yet unknown mechanisms). It is possible that some patients no longer respond to water intakes, eliminating it renally and maintaining high sodium levels. Such cases correspond to essential hypernatremia and is comparable to an osmostatic reset in which elevated odium is perceived as normal. The cause of such manifestations is the deterioration of the osmoreceptors, ADH release being conditioned by volume expansion rather than osmolarity (Stein et al, 1998). Occurrences include mentally disabled children and elderly adults. Osmostatic reset may also occur in hyponatremia, being correlated with a reduced secretion of antidiuretic hormone – ADH (Deshmukh and Thomas, 2009). To define this complex metabolic context, a hormonal profile study would be most useful. The clinical manifestations of water deficiencies are firstly neurological and include, according to the degree of dehydration, confusion, neuromuscular excitability, convulsions and coma. Research on young adults revealed that moderate

dehydration, i.e. a loss of water of 1 – 2 % of body mass, may significantly alter cognitive functions. Dehydration is associated, in infants, with irritability, confusion and lethargy, and in children with diminished cognitive performances (D'Anci et al, 2006).
It should be pointed out that the metabolic acidosis encountered in study patients is insufficiently compensated by respiration, and alkaline reserves are normal. Such conditions may be justified by water deficits (bicarbonate concentrations correspond to a smaller volume of solution, as a consequence of hydric imbalance) or may be correlated with antipshychotic, anxiolitic and anticonvulsive medication received by over 40 patients, which tend to reduce pulmonary ventilation (Garett and Grisham, 1999). Hypoventilation results in respiratory acidosis, with carbon dioxide accumulating as carbonic acid, which dissociates into H^+ and HCO_3^-. It can be concluded that, in the case of patients receiving neuroleptic medication, acidosis is mixed, but metabolically initiated. (Thabet H. et al, 2000).

CONCLUSIONS

Both mental retardation and autism spectrum disorders manifest frequent hydroelectrolitic imbalances, most common of which being hypertonic euvolemia. Although it is not possible to differentiate diagnoses solely based upon such aspects, it may be stated that hypertonic hypovolemia coupled with low and medium lactate levels are more specific to ASD. Water deficits seem due to subjects' inabilities to quench their own thirst, mostly in the case of mentally retarded, institutionalized patients. Study patients are incapable of compensating short-term hypernatremia, which allows for suspicions of osmostatic reset or volemia regulation dysfunctions (centrally or renally), i.e. an improper release of antidiuretic hormone, aldosterone and improper osmoreceptor function. Anion gaps, metabolic acidosis, hypernatremia and hypocalcemia may be perceived as side-effects of the neuroleptic medication received by numerous patients but, considering the fact that similar deviations were present in non-medicated subjects, it is debatable whether the medication is the cause or simply an aggravating factor of the condition. Further (biochemical, functional, toxicological) investigation may provide plausible data for a relevant answer. It is also recommended that, especially when administering neuroleptic medication, greater attention is paid to proper hydration. All study patients exhibited diminished calcium levels, calcium ions being significantly involved in neural excitation. The high frequency of hydric imbalances justifies further studies into the genetic aspects concerning the antidiuretic hormone, its receptors and signal transduction in MR and ASD patients.

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