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Alteration of intracranial compliance in a patient with chronic kidney disease and T1 diabetes mellitus: a case report

Alteração da complacência intracraniana em paciente com doença renal crônica e diabetes mellitus T1: um relato de caso

Distensibilidad intracraneal alterada en un paciente con enfermedad renal crónica y diabetes mellitus T1: reporte de un caso

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Abstract
Objective: The aim of this study was to relate the clinical profile with data on blood pressure (BP), intracranial pressure (ICP) and laboratory tests of a patient with Diabetes mellitus (DM) type 1 and chronic kidney disease (CKD) stage 5. Methodology: The research was carried out at the renal replacement therapy outpatient clinic of the Santa Casa de Misericórdia hospital, in Ponta Grossa-PR, previously approved by the ethics committee, under opinion nº 4,039,453. ICP monitoring and BP measurement were performed twice, on follow-up consultation days, in February and September 2020. In addition to the aforementioned parameters, a questionnaire on the patient's habits and demographic data was applied, and a consultation was carried out with the patient medical record for the collection of laboratory test data. Results: From February to September, the volunteer presented with persistent Systemic Arterial Hypertension (SAH) and hyperglycemia, and worsening of laboratory parameters. In February, the ICP morphology showed a significant change, suggesting intracranial hypertension, and the patient had a great impairment of visual acuity. In September, despite the worsening of the health condition, there was a significant improvement in vision and, also, an improvement in the ICP parameters, approaching normality. Between consultations, the diuretic administered by the patient was replaced. Conclusion: it is suggested that the visual impairment is due to intracranial hypertension and the improvement of both is related to the replacement of hydrochlorothiazide by furosemide, which occurred between consultations.
Keywords: Intracranial hypertension; Diabetic nephropathies; Furosemide; Hydrochlorothiazide.

Resumo
Objetivo: Este estudo teve como objetivo relacionar o perfil clínico com dados de pressão arterial (PA), pressão intracraniana (PIC) e exames laboratoriais de um paciente portador de Diabetes mellitus (DM) tipo 1 e doença renal crônica (DRC) estágio 5. Metodologia: A pesquisa foi realizada no ambulatório de terapia renal substitutiva, do

hospital Santa Casa de Misericórdia, em Ponta Grossa-PR, aprovada previamente em comitê de ética, sob parecer nº 4.039.453. A monitorização da PIC e a aferição da PA foram realizadas duas vezes, em dias de consultas de acompanhamento, nos meses de fevereiro e setembro de 2020. Além dos parâmetros citados, foi aplicado um questionário sobre hábitos e dados demográficos do paciente e realizada consulta ao prontuário para a coleta de dados de exames laboratoriais. Resultados: No período de fevereiro a setembro, o voluntário apresentou quadro de Hipertensão Arterial Sistêmica (HAS) e hiperglicemia persistentes, e piora dos parâmetros laboratoriais. Em fevereiro, a morfologia da PIC demonstrou alteração significativa, sugerindo hipertensão intracraniana, e o paciente apresentou grande comprometimento da acuidade visual. Em setembro, apesar da piora do quadro de saúde, houve expressiva melhora da visão e, também, melhora nos parâmetros da PIC, aproximando-se da normalidade. Entre as consultas, houve a substituição do diurético administrado pelo paciente. Conclusão: sugere-se que a deficiência visual seja decorrente da hipertensão intracraniana e a melhora de ambas esteja relacionada com a substituição da hidroclorotiazida pela furosemida, ocorrida entre as consultas.
Palavras-chave: Hipertensão intracraniana; Nefropatias diabéticas; Furosemida; Hidroclorotiazida.

Resumen
Objetivo: Este estudio tuvo como objetivo relacionar el perfil clínico con la presión arterial (PA), la presión intracraneal (PIC) y las pruebas de laboratorio de un paciente con diabetes mellitus (DM) tipo 1 y enfermedad renal crónica (ERC) en etapa 5. Metodología: La investigación se realizó en el ambulatorio de terapia de reemplazo renal, Hospital Santa Casa de Misericordia, en Ponta Grossa-PR, previamente aprobado por el comité de ética, bajo opinión nº 4.039.453. El monitoreo de PIC y la medición de PA se llevaron a cabo dos veces en los días de consultas de seguimiento en febrero y septiembre de 2020. Además de los parámetros antes mencionados, se aplicó un cuestionario sobre hábitos del paciente y datos demográficos, y se consultaron historias clínicas para recolectar datos de exámenes de laboratorio. Resultados: De febrero a septiembre, el voluntario presentó Hipertensión Arterial Sistémica (HAS) e hiperglucemia persistente, y empeoramiento de los parámetros de laboratorio. En febrero, la morfología de la PIC mostró un cambio significativo, lo que sugiere hipertensión intracraneal, y el paciente tenía un gran deterioro de la agudeza visual. En septiembre, a pesar del empeoramiento del estado de salud, se produjo una importante mejoría de la visión y, también, una mejora de los parámetros de la PIC, acercándose a la normalidad. Entre consultas se repuso el diurético administrado por el paciente. Conclusión: se sugiere que la discapacidad visual se debe a la hipertensión intracraneal y la mejoría de ambas está relacionada con la sustitución de hidroclorotiazida por furosemida, que ocurrió entre consultas.
Palabras clave: Hipertensión intracraneal; Nefropatías diabéticas; Furosemida; Hidroclorotiazida.

1. Introduction

Chronic kidney disease (CKD) is considered a public health problem worldwide and its main causes are diabetes mellitus (DM) and systemic arterial hypertension (SAH), with DM being responsible for about 30 to 50% of cases of CKD in the world (Webster et al., 2017). Diabetic nephropathy (DN) affects individuals with types 1 and 2 DM (with a higher prevalence of type 1) and known risk factors for DN include DM duration, glycemic control, blood pressure and genetic predisposition (Selby & Taal, 2020).

Latent autoimmune diabetes in adults (LADA) is a poorly studied form of diabetes, which combines characteristics of type 1 and 2 diabetes. As in type 1 diabetes, patients with LADA also have autoantibodies, however, the autoimmune process seems to be more mild, and the progression of beta cell destruction is slower, in addition, the need for insulin only occurs some time after diagnosis. Compared to type 2 diabetes, patients with LADA have lower insulin secretion, and progress to insulin dependence more quickly (Carlsson, 2019).

Diabetic Nephropathy (DN) is a microangiopathy characterized by a constant increase in albumin excretion in the urine - albuminuria (>300mg/day), associated with a decrease in glomerular filtration rate (GFR) and glomerular lesions (Sagoo & Gnudi, 2018). Although the pathophysiology of DN has not been completely elucidated, some mechanisms that trigger the disease have been described, such as: hemodynamic mechanisms, in which hyperglycemia results in an increase in glomerular pressure and also in the activation of the angiotensin II converting enzyme (causing hyperfiltration glomerular); and metabolic mechanisms (such as the polyol and hexosamine pathways), resulting in oxidative stress (OS) (Aghadavoud et al., 2017). OS induces metabolic changes in renal tissue molecules and changes in renal hemodynamics, thus being an important complicating factor in hyperglycemia (Sagoo & Gnudi, 2018).

Patients with DM are more likely to develop hypertension. This is due to the increase in peripheral vascular resistance, induced by insulin resistance and the increase in circulating volume (Ohishi, 2018). In general, in hyperinsulinemia, there is an increase in sodium reabsorption in glucose cotransport, by SGLT2 (Sodium-Glucose Co-Transporter 2), in the proximal convoluted tubule (PCT). As a result, there is a lower supply of sodium in the macula densa, inducing renin release, leading to vasoconstriction of the efferent arteriole and glomerular hypertension. Activation of the renin-angiotensin-aldosterone system (RAAS) leads to systemic vasoconstriction and activates the sympathetic nervous system, leading to increased cardiac output and peripheral vascular resistance (Seravalle & Grassi, 2016). Yet another factor that increases the volume of circulating fluid is hyperosmolarity caused by increased blood glucose levels. In this case, water and electrolytes flow from the intracellular environment to the extracellular one, raising blood pressure (Kawasoe et al., 2017).

In addition to the relationship between DN and SAH, CKD itself is a risk factor for hypertension, just as high blood pressure contributes to the progression of CKD. In general, as in DN, in CKD there is greater retention of salt and fluids, inducing the release of renin, leading to SAH. On the other hand, in SAH there is a tendency for vascular resistance (thickening and stiffness) of the renal vessels, making renal function inefficient, accelerating the CKD process (Shibata et al., 2017).

In addition to these changes related to CKD, Rickli et al., 2021 reported in their study the change in brain compliance, through noninvasive monitoring of Intracranial Pressure (ICP), in individuals with stage 5 CKD undergoing hemodialysis. The process of cerebral blood flow (CBF) autoregulation is an important factor that preserves brain volume homeostasis in changes in Cerebral Perfusion Pressure (CPP). CPP is calculated by the difference between Mean Arterial Pressure (MAP) and ICP. In autoregulation, an increase in blood pressure (BP) induces vasoconstriction of small cerebral arteries and, consequently, there is a decrease in cerebral blood volume and ICP. Self-regulation works when CPP is maintained between 50 and 150 mmHg or MAP is maintained between 60 and 160 mmHg (Armstead, 2016). However, when this mechanism is disturbed, self-regulation does not work (Stefanits et al., 2019).

In this context, this study aimed to present significant aspects of the relationship between the clinical profile with data on SAH, ICP and laboratory tests, of a patient with DM 1 and CKD stage 5.

2. Methodology

This is a qualitative-quantitative, descriptive and retrospective case report (Pereira et al., 2018), carried out after a favorable opinion from the Research Ethics Committee of the State University of Ponta Grossa (Opinion number: 4,039,453), via Plataforma Brasil. The study took place at the outpatient clinic of the Renal Replacement Therapy unit, Hospital Santa Casa de Misericórdia, in the city of Ponta Grossa-PR, and the research subject voluntarily participated in it, after signing and receiving the informed consent form (ICF).

This article reports important clinical and laboratory changes related to the occurrence of intracranial hypertension in the subject, with CKD, who was followed up between February and September 2020, in his usual consultations.

3. Results

Case description

The research subject is a white male, 45 years old, smoker, with latent autoimmune diabetes in adults (LADA) for about 10 years (a form of DM1), high blood pressure and stage 5 CKD. Regularly monitored at the outpatient clinic of the Renal Replacement Therapy (RRT) unit of Hospital Santa Casa de Ponta Grossa - PR, he performed laboratory tests and medical consultation every six months. The results of laboratory tests are shown in Table 1, as well as the estimated

Glomerular Filtration Rate (GFR) for the patient. In April 2021, the patient started hemodialysis, starting to attend the RRT three times a week.

Table 1. Results of laboratory tests, glomerular filtration rate and CKD stages.

Laboratory Tests							
Date	June/18	Feb/19	Aug/19	Feb/20	Aug/20	Nov/20	Feb/21
Fasting glucose (mg/dL)	**301**	**273**	**156**	**156**	**141**	-	-
HbA1c (%)	**11.40**	**10.40**	**8.50**	**7.50**	**8.40**	**9.40**	**9.40**
Creatinine (mg/dL)	**1.62**	**2.09**	**2.41**	**2.85**	**3.14**	**4.41**	**6.45**
Calcium (mmol/L)	-	**9.45**	**8.55**	-	-	-	1.046
Phosphor (mg/dL)	-	4.01	3.69	-	-	4.41	4.06
Potassium (mmol/L)	**6.1**	**5.59**	**5.5**	**5.41**	**5.9**	**5.37**	**6.22**
Sodium (mmol/L)	135	137	137	141,1	135	-	-
Urea (mg/dL)	**50**	**50**	**46**	**49**	**78**	-	-
Hemoglobin (g/dL)	12.9*	11.13*	12.1*	10.6*	10.4*	10.2*	-
Ferritin (ng/mL)	-	**395.3**	336	-	**366.3**	**413.2**	311.7
Iron (µg/dL)	-	82	80	-	101	-	-
Transferrin Saturation	-	42.60	34	-	49.4	45.80	43.00
Microalbuminuria	**4136**	**2614**	**2739**	**2355**	**3966**	-	-
Platelets (µ/L)	350000	313000	329000	308000	309000	-	-
Leukocytes (µ/L)	9070	7300	8710	6790	-	-	-
Parathormone (pg/mL)	-	36	69	-	-	63	**94**
Vitamin D3 (ng/mL)	-	-	15.4*	-	-	25.3	31.7
Total Cholesterol (mg/dL)	194	183	130	127	124	-	138
Triglycerides (mg/dL)	157**	159**	-	89	74	-	95
HDL (mg/dL)	38*	31*	31*	32.2*	38,6*	-	38*
LDL (mg/dL)	125	120	76	77	70	-	81
Estimation of Glomerular Filtration Rate							
CKD-EPI (ml/min/1.73	**51.6**	**37.6**	**31.7**	**25.7**	**22.8**	**15.0**	**9.5**
Stages of Chronic Kidney Disease							
Stage	**3a**	**3b**	**3b**	**4**	**4**	**4**	**5**

Values in bold indicate those above the reference values. * Indicates values below reference values. ** Indicates boundary values. - Indicates the absence of data record. Source: Authors (2021).

During the period Aug/2019 - Aug/2020, the patient used losartan 100 mg/day, hydrochlorothiazide 25 mg/day, simvastatin 20mg/day, insulin glargine and aspartame, as needed, according to tests. As of Aug/2020, there was a change in the prescription in which hydrochlorothiazide 25 mg/day was replaced by furosemide 40 mg/day. After the exams in Nov/2020, the concentration of losartan prescribed decreased to 50 mg/day, and furosemide started to be used on alternate days.

He had impaired visual acuity as a result of Diabetic Retinopathy (DR) with the presence of optic disc neovessels, having already undergone surgical treatment. With complaints of frequent headaches and throbbing pain. The patient had his intracranial pressure (ICP) monitored non-invasively (Brain4care®) twice, the first monitoring took place in February/2020 and the second in September/2020, the results of these two monitoring are presented in Table 2, through P2/P1 ratio, Time to peak (TTP) and number of pulses collected.

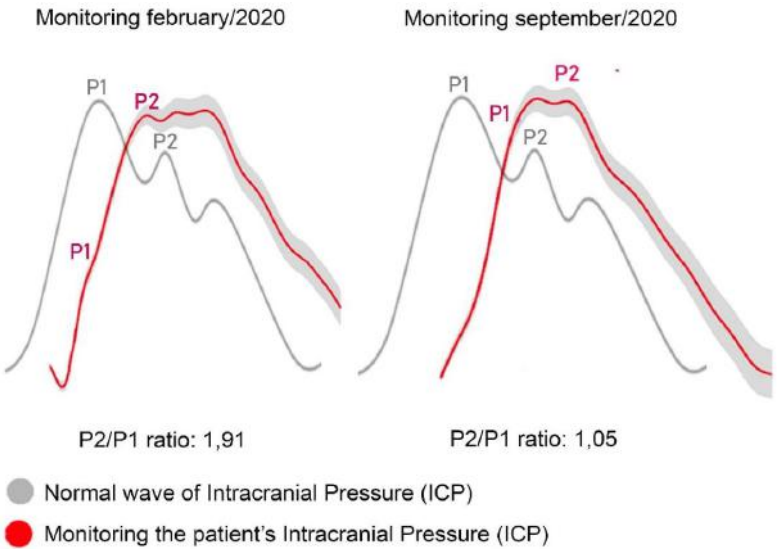
Table 2. Results of intracranial pressure monitoring and blood pressure measurement.

Intracranial Pressure Monitoring				
Date	Feb/2019	Feb/2020	Sept/2020	Nov/2020
Average P2/P1 Ratio	-	**1.91**	**1.05**	-
Average TTP	-	**0.491**	0.168	-
Average of the number of pulses collected	-	65	66	-
Physical exam				
Blood pressure (mmHg)	**140x80**	**154x101**	**192x114**	100x70

Values in bold indicate those above the reference values. - Indicates the absence of data record. Source: Autors (2021).

The monitoring method used, Brain4care®, provides the results through the morphology of the ICP waves, using sensors that detect micro deformations in the skull (Mascarenhas et al., 2012). Under normal conditions, the relationship between the peaks is P1>P2, and when there is an increase in ICP and a decrease in brain compliance, the morphology of this wave is gradually altered, increasing the P2/P1 ratio, with the eventual overcoming of the P1 peak by the P2 peak (Ballestero et al., 2017). Figure 1 shows the ICP waves collected in February and September, compared to what is considered a normal intracranial pressure wave, that is, a wave in which peak P2 is higher than peak P1.

Figure 1. Comparison between the normal intracranial pressure wave and the waves obtained from patient monitoring.



Source: Authors (2021).

Table 2 also presents the number of pulses collected, which indicates the quality of the sample. Samples with a reduced number of pulses and with the presence of artifacts were discarded by the equipment's analysis system (Brain4care®). The TTP indicates the time from the beginning of the wave to the appearance of the highest peak, being an auxiliary parameter in the study of intracranial compliance, and there are still no reference values published in the literature. This parameter represents the resistance of blood entering the brain and the normal value is 0.25, as reported by Thaíse Costa (Research Coordinator at the Brain4care Scientific Department, personal communication, September 29, 2020). Higher values are considered pathological.

4. Discussion

DM is responsible for many secondary diseases, including neurological diseases, being also associated with more severe outcomes and the mechanism by which DM causes neurological deterioration is not well known. Onodera et al. (2012), from a study carried out in rats, demonstrates that DM causes thickening by fibrous collagen of the basement membrane of the brain microvasculature, and an increase in the P2 peak in diabetic rats during continuous fluid injection, findings that support the evidence of decreased brain compliance in diabetic rats.

Laboratory data show that the subject of this research presented high blood glucose concentrations during the evaluated period, especially demonstrated by the glycated hemoglobin (HbA1c) test. Likewise, a change in the conformation of the ICP waveform was observed in both monitoring, with peak P2 being greater than peak P1, while under normal conditions the ratio should be P1>P2, with the calculated value of this ratio being less than 1 (P2/P1<1) (Rickli et al., 2021).

Regarding the cerebral autoregulation process, despite the MAPs, in the two situations in which the patient's ICP was monitored, falling within the aforementioned range of values of cerebral autoregulation (118.6 mmHg and 140 mmHg, respectively), we can conclude that there was change in the patient's brain compliance, considering the important change in ICP.

Comparing the ICP monitoring (Figure 1), the monitoring carried out in February/2020 showed a wave with more pronounced pathological characteristics than the result obtained in the monitoring of September/2020, which presented a morphologically abnormal wave, but, taking into account the mean of the P2/P1 ratio, the result (P2/P1=1.05) was closer to normality (P2/P1<1). The TTP (Table 2) was higher in the first monitoring (0.491) in relation to the second (0.168), corroborating the results of the P2/P1 ratio. With the progression of CKD, and the worsening of laboratory parameters (Table 1), it was expected that the results related to ICP and brain compliance would follow the general condition of the patient, that is, show a worsening as the consolidation of the worsening of the case and the approximation of CKD to stage 5, however, was not what we recorded.

The use of antihypertensive drugs in patients with CKD is called conservative treatment of renal failure, as it aims to delay the progression of renal disease, since hypertension in CKD involves the expansion of extracellular fluids due to the decreased ability to sodium excretion by the kidneys, therefore, diuretics are widely used in these patients. Loop diuretics such as furosemide are often the choice because they increase sodium excretion by about 20% and are effective at any GFR. On the other hand, thiazides (hydrochlorothiazide is an example) are less used, as their effectiveness is reduced in GFRs below 40mL/min. However, some authors dispute this information, and claim that, due to their long duration, thiazides still prevent rebound antinatriuresis (Dussol et al., 2005).

During the first monitoring, the patient was being treated for arterial hypertension with losartan 100 mg/day and hydrochlorothiazide 25 mg/day for about a year, and during the second monitoring, he was using losartan 100 mg/day and furosemide 40 mg/day for about 15 days. Thus, we believe that the use of furosemide may have had a positive influence, decreasing the patient's ICP, decreasing the value of the P2/P1 ratio in the second monitoring. Currently, the drug most used in the treatment of intracranial hypertension is mannitol and, in the study by Aboelela & Alrefaey (2020), furosemide showed the same capacity as mannitol, but with better hemodynamic stability and less hydroelectrolytic disturbance, being effective in reducing edema brain.

On the day of the first ICP monitoring, the patient reported that he routinely presents with symptoms that corroborate intracranial hypertension. Complaints included intense and recurrent headaches of a pulsating type, accompanied by photophobia, phonophobia and visual tremor. According to Friedman, 2019, headache is the most common symptom in individuals who have Idiopathic Intracranial Hypertension (IIH). Symptoms most often associated with headache include photophobia (70%) and phonophobia (52%); in addition to nausea (47%) and emesis (17%). Curone et al. 2015 do not consider

pulsatile headache as a symptom of IIH, however, the patient who presents this type of pain can also be affected by a primary headache. In addition to these symptoms, the patient has impaired visual acuity, diagnosed with DR. This condition has been especially noted for its possible relationship with intracranial hypertension. On the day of the first ICP monitoring, in which the P2/P1 ratio was significantly altered, the patient reported that he was partially blind, with only 20% of his visual capacity, requiring a companion to carry out his activities. In the second monitoring, in which the P2/P1 ratio was close to normal, he reported that his vision had improved significantly, denoting autonomy in his actions (however, he was unable to inform the percentage of visual capacity). Still, he said that in October 2019 he underwent surgery to treat eye hemorrhage, but he was unable to give more details about what happened.

Between the dates of the monitoring, the patient underwent a standard treatment of DR, with laser beams. Although improvement may be primarily associated with treatment, intracranial hypertension is known to lead to optic disc edema. The optic disc is a portion of the optic nerve, formed by the junction of the axons of the retinal ganglion cells. When swollen, it induces various visual disturbances, including transient visual obscuration, visual field defects and even blindness. Optic disc and retinal hemorrhages are also common in this condition. Visual symptoms can often be reversed by lowering ICP to a normal level, provided it is maintained (Hayreh, 2016). The patient's clinic is consistent with the findings in the literature for optic disc edema, from ocular hemorrhage to compromised visual acuity. Furthermore, the disturbances were significantly improved with the normalization of ICP, reinforcing the possibility that the patient's loss of visual acuity was caused by intracranial hypertension.

5. Conclusion

The present study highlights the importance of the relationship between ICP and CKD and DM, considering that, despite not having been a parameter discussed in these cases for many years, based on new non-invasive monitoring techniques, this clinical parameter has been showing its relevance. ICP shows an inherent relationship with the pathophysiology of many clinical conditions, and in this study we could observe a possible relationship between intracranial hypertension, diabetes and the patient's vision disorders, as well as a possible direct impact of the medication used in its treatment on the decrease of intracranial pressure (ratio P2/P1).

It is recommended that new studies be carried out that include a greater number of subjects, in order to clarify the relationship between ICP in CKD and DM conditions and other clinical manifestations of the sampled individuals.

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