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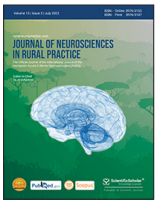

Original Article

Electrocardiographic changes in patients with raised intracranial pressure from supratentorial brain tumors

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ABSTRACT

Objectives: A wide variety of electrocardiographic (ECG) changes has been described in the context of neurological catastrophe. There has been diverse and plentiful literature emphasizing the cardiac changes in acute cerebrovascular events and traumatic brain injury. In stark contrast, there is scarce literature on the incidence of cardiac dysfunction caused by raised intracranial pressure (ICP) resulting from brain tumors. The study aimed to observe the ECG changes concurrent with intracranial hypertension resulting from supratentorial brain tumors.

Materials and Methods: This is a pre-specified subgroup analysis of a prospective and observational study on cardiac function in patients presenting for neurosurgery. Data of 100 consecutive patients of either sex between 18 and 60 years who presented with primary supratentorial brain tumors were analyzed. The patients were divided into two groups: Group 1 consisted of patients without clinical and radiological features of raised ICP and Group 2 consisted of patients with clinical and radiological features of raised ICP. A 12-lead ECG was obtained for every patient on the day before the neurosurgical procedure as part of the pre-anesthetic assessment. The cardiologist and the neuroanesthetist independently examined the ECG, and it was then classified and coded as per the standardized Minnesota code. Statistical analysis was performed with IBM SPSS (release 22.0; IBM Corp., Armonk, NY, USA). The normality of the distribution of continuous variables was tested using the Shapiro–Wilk test. Normally distributed variables were expressed as Mean ± SD. All nominal or categorical variables are described as frequencies and percentages. Categorical variables were compared using the Chi-square test or the Fisher's exact test. The normally distributed continuous variables were compared using Student's *t*-test. "$P < 0.05$" was considered statistically significant.

Results: About 6% in Group 1 and 32% in Group 2 had abnormal ECG. This was significantly different in Group 2 compared to Group 1 ($P < 0.05$). No patients in Group 1 had sinus bradycardia, whereas it was observed in 12% of the patients in Group 2 ($P = 0.02$). ST-segment depression was found in 12% of patients in Group 2, whereas none had it in Group 1 ($P = 0.02$). ST-segment elevation was noticed in 16 % in Group 2 and 2% in Group 1 ($P = 0.01$). T-wave abnormalities were found in 16% compared to 4% in Group 1 ($P = 0.03$).

Conclusion: In patients with supratentorial tumors, we observed that those with raised ICP had a higher incidence of ECG changes than those with normal ICP. In addition, repolarization abnormalities and arrhythmias were significantly higher in patients with raised ICP.

Keywords: Brain tumor, Electrocardiography, Intracranial pressure, Supratentorial

INTRODUCTION

A wide variety of electrocardiographic (ECG) changes has been described in the context of neurological catastrophe.[1-3] Sympathetic overactivity is the most plausible cause of the significant cardiac pathologies in acute neurological conditions such as aneurysmal subarachnoid hemorrhage, traumatic brain injury (TBI), and stroke.[1,2,4,5] ECG, being one of the windows to autonomic activity, has provided some crucial evidence to suggest the pathophysiological mechanism of cardiac dysfunction due to neurological insults.[1] The most common changes described in the context of neurocardiology are arrhythmias and repolarization abnormalities.[1,6-8] Some of these changes, such as ST-segment elevation/depression, may be indistinguishable from those seen in patients with an acute myocardial ischemic event.[1,8,9] Therefore, it is of paramount importance that the clinician is able to distinguish the ECG changes caused by neurological conditions from that of ischemic heart disease.

There has been diverse and plentiful literature emphasizing the cardiac changes in acute cerebrovascular events and TBI. In stark contrast, there is scarce literature on the incidence of cardiac dysfunction caused by raised intracranial

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pressure (ICP) resulting from brain tumors. Therefore, the study aimed to observe the ECG changes concurrent with intracranial hypertension resulting from supratentorial brain tumors.

MATERIALS AND METHODS

This is a pre-specified subgroup analysis of a prospective and observational study on cardiac function in patients presenting for neurosurgery. After obtaining approval from the Institutional Ethics Committee, the study was initiated.

In this prospective and observational study, 126 consecutive patients of either sex between 18 and 60 years who presented with primary supratentorial brain tumors for elective neurosurgery were screened for eligibility based on the inclusion and exclusion criteria (subsequently described). The presence of clinical features of raised ICP such as headache, vomiting, and papilledema was assessed by the neurosurgeon and the neuroanesthetist. The location of the lesion and radiological evidence of raised ICP was determined by a neuroradiologist from computed tomography or magnetic resonance imaging based on parameters such as cerebral edema, midline shift >5 mm, hydrocephalus, and gray-white matter effacement. After a detailed evaluation, the patients were divided into two groups based on the clinical and radiological features of raised ICP. Group 1 comprised patients with no clinical or radiological evidence of raised ICP and Group 2 included patients with both clinical and radiological features of raised ICP.

Patients with diabetes mellitus, hypertension, vascular diseases, chronic obstructive pulmonary disease, baseline electrolyte abnormality, known cardiac ailments (coronary heart disease, valvular heart disease, congenital heart disease, and congestive heart failure), and a prior history of chemotherapy or radiotherapy were excluded from the study. In addition, those who were American Society of Anaesthesiologists (ASA) physical state Class III, IV, and V patients were also excluded to avoid potential bias in the results. Before commencement of the study, informed consent was obtained from either patients or the next of kin.

ECG recording

A 12-lead ECG was obtained for every patient on the day before the neurosurgical procedure as part of the pre-anesthetic assessment. The cardiologist and the neuroanesthetist independently examined the ECG during the routine pre-operative assessment. The ECG was coded as per the standardized Minnesota code.[10] The pooled abnormal ECGs were further classified as (A) cardiac arrhythmia, (B) ventricular repolarization disorder, (C) conduction disorder, and (D) others.

Statistical analysis

Analysis was performed with IBM SPSS (release 22.0; IBM Corp., Armonk, NY, USA). The normality of the distribution of continuous variables was tested using the Shapiro–Wilk test. Normally distributed variables were expressed as Mean ± SD. All nominal or categorical variables are described as frequencies and percentages. Categorical variables were compared using the Chi-square test or the Fisher's exact test. The normally distributed continuous variables were compared using Student's *t*-test. "$P < 0.05$" was considered statistically significant.

RESULTS

Out of the enrolled 126 patients, clinical data of 100 patients with ECG recordings were taken for analysis. Twenty-six patients were excluded after assessing for inclusion/exclusion criterion, incomplete data, or absence of good quality ECG. There was statistically no significant difference ($P > 0.05$) between the two groups in terms of demographic characteristics such as age, weight, height, body mass index, and body surface area [Table 1]. There was no preponderance of any particular tumor, and they were of varied types such as meningiomas, gliomas, ependymoma, and DNET [Table 2].

Incidence of ECG abnormalities

The analysis of baseline ECG parameters showed that the patients in Group 2 had a significantly higher incidence of abnormal ECG (32%) as compared to patients in Group 1 (6%) ($P = 0.000$).

The ECG classified as per the Minnesota code is shown in [Table 3].

The ECG abnormalities were further categorized as follows:

1. Cardiac arrhythmias: Sinus bradycardia was found in 12% in Group 2 ($P = 0.02$), whereas none of the patients in Group 1 had the same. Ventricular premature complexes were found in 4% in Group 2, but this was not significant.

Table 1: Comparison of basic demographic data in the two groups.

Variables	Group I (*n*=50)	Group II (*n*=50)	P
	Mean±SD	Mean±SD	
Age (years)	35.5±9.6	38.5±9.8	0.241
Weight (kg)	65.7±9.3	62.5±10.0	0.214
Height (cm)	164.3±6.9	162.2±9.8	0.349
Body surface area (/metre^2)	1.7±0.1	1.7±0.2	0.211
Body mass index (kg/m^2)	24.3±2.9	23.7±2.9	0.433
Male/female	25/25	27/23	0.889

2. Ventricular repolarization disorders: ST-segment depression was found in 12% in Group 2, whereas none of the patients in Group 1 had the same ($P = 0.02$). ST-segment elevation was observed in 16% in Group 2 versus 2% in Group 1 ($P = 0.01$). T-wave abnormalities were found in 16% in Group 2 compared to 4% in Group 1 ($P = 0.03$). The repolarization changes were not confined to any specific leads.
3. Conduction disorders: Although QT prolongation was found in 6% of the patients in Group 2, this was not statistically significant.
4. Others: The left QRS axis deviation was found at 10% in Group 2; however, this was not significantly different from Group 1.

Table 2: Neurosurgical diagnosis of patients in each group.

Diagnosis	Group 1 (normal ICP)	Group 2 (raised ICP)
Parasagittal meningioma	5	7
Parafalcine meningioma	5	7
Occipital meningioma	3	3
Frontal epidermoid tumor	3	-
Parietal ependymoma	3	-
Frontal glioma	8	5
Temporal glioma	7	-
Parietal glioma	8	5
Thalamic glioma	1	-
Frontal DNET	5	-
Temporoparietal glioma	-	6
Parieto-occipital glioma	-	6
Parietal DNET	2	-
Craniopharyngioma	-	2
Third ventricular colloid cyst	-	7
Choroid plexus papilloma	-	1
Third ventricular ependymoma	-	1
	Total 50 (100%)	Total 50 (100%)

ICP: Intracranial pressure

DISCUSSION

ECG changes in acute brain injury such as TBI, SAH, and stroke have been described in the literature, wherein common manifestations included arrhythmias and repolarization abnormalities.[1] However, there has been sparse literature on the ECG changes in the setting of brain tumors. We studied the ECG changes in patients with supratentorial brain tumors and found that 32% of patients with raised ICP had ECG changes compared to 6% of patients without raised ICP.

We observed that among patients with raised ICP, 12% had bradycardia. A sudden acute increase in ICP elicits the Cushing's triad of hypertension, bradycardia, and irregular breathing. It is traditionally believed to be due to ischemia of the brainstem-inducing sympathetic overactivity. The massive intrinsic activation of the sympathoexcitatory neurons of the ventrolateral medulla is believed to be the mechanism of this terminal response.[11] Fitch *et al.* described the sequence of events from the start of a rise in ICP. The bradycardia component was identified as the first of six events which included bradycardia, arrhythmia, pupillary constriction, unilateral pupillary dilatation, and systemic hypertension.[12] A few studies have recently shown that Cushing's response is a part of a pathophysiological reflex response for blood pressure regulation rather than a last-ditch phenomenon.[13-15] It has been shown in recent studies that a gradual, modest increase in ICP can cause an

Table 3: ECG changes classified as per Minnesota code for Group 1 and Group 2.

ECG changes	Group 1		Group 2		*P*-value
	Frequency	Percentage	Frequency	Percentage	
Q and Qs patterns	1	2	4	8	0.16
Left QRS axis deviation	0	0	5	10	0.056
High-amplitude R waves	0	0	0	0	
S-T segment depression	0	0	6	12	0.02
T wave abnormality	2	4	8	16	0.03
U amplitude >1 mm	0	0	5	10	0.056
AV conduction defect	0	0	1	2	1
Sinus tachycardia (heart rate >100 beats/min)	3	6	6	12	0.29
Sinus bradycardia (heart rate <50 beats/min)	0	0	6	12	0.02
Frequent premature atrial, nodal, or ventricular beats	2	4	3	6	1
Q-Tc >0.44s	0	0	3	6	0.24
ST-elevation	1	2	8	16	0.01
Abnormal ECG	3	6	16	32	0.000
HR	73.7±8.5		70.6±11.8		0.09

ECG: Electrocardiographic

increase in sympathetic activity and a change in heart rate variance.[14,15] Another plausible reason is that raised ICP can stimulate the trigger zones of the central autonomic network producing a bradycardiac response.[7,8,16] Stimulation of the anterior hypothalamus, the left insula, and the orbitofrontal cortex has been found to cause bradycardia.[7,8] Other studies have reported incidence of sinus bradycardia in 4–12% of patients with brain tumors.[17-19]

In our study, the repolarization abnormalities, that is, ST-segment depression, ST elevation, and T-wave changes, were found in 12, 16, and 16%, respectively, of Group 2 patients. The cellular mechanism for the repolarization changes in acute neurological conditions has been attributed to the sympathetic hyperactivity and the resultant release of large volumes of norepinephrine from the sympathetic nerve terminals.[1,5] Norepinephrine stimulates the synthesis of adenosine 3,5 cyclic phosphate, which causes the opening of the calcium channel with an influx of calcium.[20] The inward movement of calcium has two consequences; first, it causes the efflux of potassium; this could potentially explain the cerebrogenic peaked T waves. Second, it also results in the actin and myosin interaction; however, the failure to close calcium channels ultimately results in cardiac cell death.[1] This pathophysiological cascade explains the cardiac toxicity that ranges from brief bursts of ECG abnormalities to the hyperkalemic pattern of peaked T waves and then finally to permanent repolarization abnormalities (such as ST-segment and T-wave changes and U waves) reflecting cell death.[1,3] The histological changes of transmural cardiac necrosis correlate with the Q waves seen on the ECG.[1,20] In our study, though 8% of the patients in Group 2 had Q waves, it was not statistically significant.

Our results of significant repolarization changes and arrhythmias are similar to that of a few studies which observed ECG changes in the setting of brain tumors. Póvoa *et al*. studied ECG changes in various neurological conditions and found that in patients with brain tumors, 24% had non-specific ST-T abnormalities, 7.5% had features of subendocardial ischemia, 3% had prolonged QT interval, and 3% had ST elevation.[18] However, their study did not specify whether tumors were limbic/extralimbic, supratentorial/infratentorial, and whether they had raised ICP or not. The influence of each of these factors has to be considered while studying ECG changes in patients with brain tumors. Rudehill *et al*. compared ECG changes between patients with SAH and brain tumors and divided each group into subgroups based on the presence and absence of cardiovascular comorbidities.[17] In the tumor group without comorbidities and electrolyte changes, 56% had an abnormal ECG. About 11% presented with T-wave abnormality, 9% had ST-segment depression, prolonged QT interval was found in 4.6%, and U waves were found in 9%.[8] Their study did not categorize whether the patients had raised ICP or not; furthermore, both supratentorial and infratentorial tumors and those involving the central autonomic network were included in the study. Hersch found that among patients with intracranial space-occupying lesions, 5% had prolonged PR interval, 15% had ST elevation, and 15% presented with T-wave abnormality.[21]

In contrast to the above studies, which observed ECG changes in brain tumors without delineating supratentorial versus infratentorial, limbic versus extra limbic, raised ICP versus normal ICP, we included only patients with supratentorial tumors and further divided them into two groups based on clinical and radiological features of raised ICP. Our main aim was to find out the impact of intracranial hypertension on cardiac electrical activity. Infratentorial lesions compressing the brainstem could produce a myriad of ECG changes regardless of the presence or absence of raised ICP. We also excluded patients with lesions involving the central autonomic network such as the insular and medial prefrontal cortices, the amygdala, and the hypothalamus to remove the influence of these confounding factors on the study results. These regions could produce cardiac changes as part of a central autonomic network, independent of whether they cause raised ICP.[1,7,8] A retrospective analysis by Koepp *et al*. studied the effects of the limbic system on ECG changes in the setting of brain tumors. They observed that 40% of patients with brain tumors had ECG changes, especially QTc prolongation. They noted that tumors involving the limbic system had a higher percentage (72%) of ECG abnormalities compared to the extra limbic system(27%).[19]

In this context, it is essential to know the incidence of ECG changes in other neurological conditions and how it differs from the findings in patients with brain tumors.[22] In TBI, the incidence of ECG changes has been described as between 48% and 99%. In one of the largest series of TBI patients, repolarization abnormalities were present in more than half of the patients.[23] Conduction disorders such as QT prolongation and arrhythmias were observed in 38% of patients. ECG abnormalities in SAH have been reported as between 49% and 100%.[24] The ST-segment changes have been observed in 15–51% of patients, T-waves in 12–92%, and U-waves in 4–47%. QT prolongation was the most common conduction disorder, found in 11–66% of the patients.[25] Although the melange of ECG changes in these conditions and brain tumors encompasses repolarization changes and arrhythmias, the lesser incidence of ECG changes observed in our study could be because brain tumors, in contrast to pathologies such as SAH, TBI, and stroke, do not produce an acute increase in ICP.

An acute rise in ICP has been shown to affect cardiac functions due to brain ischemia and the associated increased sympathetic activity or, in severe cases, sympathetic storm. Shivalkar *et al*. studied canine models of increased ICP and demonstrated a 1000-fold increase in serum levels of

epinephrine after brain death.[4] The same study explored the variable effects of rapid versus slow rise in ICP on the myocardium. Cardiac histology in the dogs with an acute increase in ICP revealed substantial pathologic myocardial ischemia. In contrast, canines with a gradual rise in ICP showed a lesser increase in serum epinephrine levels.

Similarly, transmurally scattered foci of myocardial injury were found in patients dying from acute intracranial lesions large enough to produce acute increases in ICP, such as intracranial bleeding and massive ischemic edema.[4,20] These cardiac lesions were not found in slowly progressive tumors unless additional factors such as hemorrhage into a tumor or inflammatory edema superimposed an acute rise in ICP.[4,12,26] It is generally perceived that in patients whose ICP raises slowly, significant clinical cardiac effects are not seen. Hence, in situations like slow progressive increase in ICP, like in the case of brain tumors, the impact of ICP on cardiac function has not been extensively studied. However, a recent study by Koszewicz *et al*. in patients with brain tumors has found that heart rate variability was low, and the low-frequency/high-frequency ratio was higher in patients with brain tumors which indicated sympathetic hyperactivity.[27] This study suggests that the plausible causative factor of cardiac dysfunction in patients with intracranial hypertension due to brain tumors could be sympathetic hyperactivity. Although our study cannot conclusively elucidate the causal relationship between ECG changes and sympathetic activity, the similarity of ECG changes to that in SAH and TBI signposts toward this.

The implications of ECG changes in our study population are many. During the perioperative period, serum electrolytes should be maintained at normal levels, particularly magnesium and potassium. This is imperative to minimize contributions of dyselectrolytemia to arrhythmias and repolarization abnormalities of neurocardiac etiology, and detected arrhythmias should be managed appropriately. The presence of sinus bradycardia warrants cautious use of vagomimetic drugs such as fentanyl, propofol, and vecuronium for induction and maintenance of anesthesia in such cases.[28] The prognosis of patients with acute neurovascular diseases has been significantly worsened by the presence of an arrhythmia. Mortality in all patients was increased when a "malignant" ventricular arrhythmia was detected.[16,29-31] ECG changes such as prolonged QTc and ventricular extrasystolic beats have also led to worse outcomes.[31] We did not find the occurrence of any malignant arrhythmias in our study group.

The relevance of changes during the repolarization period is that an extrasystole could produce malignant arrhythmias such as ventricular tachycardia and fibrillation during this vulnerable period. Thus, abnormalities in repolarization are often described as potentially the most lethal features of the ECG in the setting of neurological disease. The changes are observed mainly in the anterolateral or inferolateral leads; this could be misinterpreted as subendocardial infarction or anterolateral ischemia.[1,8] The significance of such misreading is that treatment such as antiplatelet therapy and fibrinolytic may be commenced, which is understandably not warranted in such scenarios. Yogendranathan *et al*. reported a case of frontoparietal meningioma where ST elevation in inferior leads prompted management with antiplatelet therapy and unfractionated heparin.[9] Interestingly, there was no concomitant troponin elevation, and the ECG changes persisted despite the treatment with heparin. This was further complicated by hemorrhage into the tumor and worsening of GCS. The differences between myocardial ischemia and neurogenic cardiac disease are significant.[7] With ischemic disease, myocardial necrosis occurs in the compromised vascular territory. In contrast, in the neurogenic stunned myocardium, the myocardial changes reflected by the regional wall motion abnormalities extend beyond a single epicardial vascular distribution and are reversible.[1,7,8,32] In our study, the repolarization changes were not confined to any specific lead and were largely non-specific.

ECG changes, being a window to the cardiac function, warrant further studies with echocardiographic evaluation to assess whether these patients have evidence of cardiac dysfunction. The presence of cardiac dysfunction in this patient population would necessitate prudent anesthetic management. In vulnerable neurosurgical patients, maintaining hemodynamic stability is imperative to prevent impaired cerebral perfusion/oxygenation and secondary neuronal injury. Events that could elicit a stress response and catecholamine surge can precipitate cardiac dysfunction and thus should be managed cautiously during the perioperative period.[7,8]

Limitations

We compared patients with raised ICP and without features of raised ICP to find the effect of intracranial hypertension on cardiac function. We included patients of ASA I and II only. However, including ASA III patients could have helped generalize the results better. Furthermore, as our center is cardiac and neurosciences center, we could not add non-neurological pre-operative patients as a control group.

We did not quantitatively measure ICP and relied on clinical and radiological features as evidence for raised ICP. All the patients in Group 2 had large lesions and conclusive evidence such as midline shift >5 mm, hydrocephalus, loss of gray-white matter differentiation, effacement of ventricles, and basal cisterns. However, measurement of ICP through intraoperative subdural ICP catheter or optic nerve sheath diameter could have been a better and more efficient method to determine raised ICP.

We excluded patients with lesions in the prefrontal cortex, insula, hippocampus, amygdala, and hypothalamus. These regions, part of a central autonomic network, can produce cardiac changes, independent of whether they cause raised ICP. However, we cannot completely rule out the influence of the same in the study, for example, hydrocephalus of the third ventricle from a craniopharyngioma could cause compression of the hypothalamus. A frontal and temporal tumor could cause pressure effects on the prefrontal cortex and insula. It is clinically near impossible to rule out the complete influence of the central autonomic network on the impact on cardiac function in patients with raised ICP.

We did not take a post-operative ECG to identify whether the changes seen were reversed following tumor resection. Similarly, we did not correlate the changes with echocardiography or measure markers of cardiac dysfunction such as troponin and pro-brain natriuretic peptide in this study. The future observational studies which would eliminate these limitations are required. Furthermore, studies assessing the relation between ECG changes and the prognosis of patients in the context of brain tumors are currently lacking and would be beneficial.

CONCLUSION

We aimed to evaluate the incidence of ECG changes in patients with raised ICP due to supratentorial brain tumors in this study. We observed a higher incidence of ECG changes in patients with raised ICP than those with normal ICP. In addition, repolarization abnormalities and sinus bradycardia were significantly higher in patients with raised ICP. Further studies are required to elucidate a causal relationship between raised ICP and ECG changes and whether the ECG changes can be used for prognostication.

Declaration of patient consent

The authors certify that appropriate consent has been obtained from all participants.

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Conflicts of interest

There are no conflicts of interest.

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