

Depression and dementia from hyponatremia in brain cancer patients exposed to frozen food chemicals

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Abstract: Frozen food chemicals contain neurotoxins which disturb electrolyte levels. Altered electrolyte levels can induce mental illnesses. This study was focused on finding the prevalence of depression, dementia, intake of antidepressants and electrolytic alterations in brain cancer (BC) patients and in control group (CG) who were taking frozen and canned food. The levels of electrolytes were compared in both groups through Mann-Whitney U test. The Odds Ratio (OR) and Relative Risks (RR) were calculated of having a specific occurrence or condition of brain cancer patients vs. controls. Majority (41.42%) patients were from the age group 33-57 years. There were 52% male and 47% female patients. There was more occurrence of dementia (41%) and depression (6%) in patients as compared to CG. 94% patients were found with dementia. 32% patients were having low levels of sodium and 43% were having low levels of potassium. High levels of potassium (26%) were found in CG. 76% patients and 73% controls were taking canned food in moderation. 69% patients and 50% controls were taking frozen food in moderation. The potassium levels (p value: 0.00001) and sodium levels (p value: 0.01468) were found at significant difference in brain cancer patients and control group. Statistically significantly higher odds of outcome (OR>1) and increased relative risks (RR) were reported in dementia, depression and intake of anti-depressants for BC vs. CG. This epidemiological study reports hyponatremia as a significantly different parameter between brain cancer patients and controls. Food's chemicals induce hyponatremia, which can disturb mental states to develop different neurological conditions.

Keywords: Brain cancer, anti-depressants, depression, frozen food, sodium chemical, hyponatremia, hyperkalemia.

INTRODUCTION

A shift in diet from organic to preserved frozen food has raised different mental health concerns in the form of depression, and hence the intake of antidepressants are now in use. These processed items loaded with neurotoxic chemicals (El Hefny *et al.* 2017). Disturbances and abnormalities in electrolyte functions have also been reported from mentally imbalanced people. Electrolytic balance is indispensable in the central nervous system (CNS) to regulate the mental performance. Its imbalance can result in severe neurological diseases (Riggs, 2007). Altered levels of serum sodium provoke neuronal depression or neuronal irritability. In processed frozen-preserved foods, several food chemicals are being in use as antimicrobial agents to increase shelf lives of the products. Freezing is as an efficient method to preserve meat, but it can destroy the muscle fibers of it because of the ice crystal formation (Sebranek, 1982). Sodium benzoate as a frozen food chemical is a potent neurotoxin, which induces negative effects on learning and memory performance (Khoshnoud *et al.* 2017). Propionic acid has

a detrimental immunosuppressive effect on body against bacteria, viruses and tumor cells (Kundu *et al.* 2016). Potassium sorbate is proved to induce genotoxic effects on human lymphocytes *in vitro* (Mamur *et al.* 2010). The blanching process before freezing results in a reduction in the nutritional value of food (Arroqui *et al.* 2002). The incidence ratio of dementia in Pakistani population was observed at 172.01 per 10,000 individuals (Shaukat *et al.* 2016). According to Akman *et al.* (2010), only 15% population consumes the recommended daily amount of fresh fruits and vegetables. A balanced nutrition is required for proper human mental performance (Arvidsson *et al.* 2017). The neuropsychological and neurodegenerative diseases in old age originate from the lack of a proper balanced diet (Bourre, 2006). An unhealthy dietary habits increase the susceptibility of depressive illness (Puloka *et al.* 2016). The current study focused on finding the prevalence of dementia, depression, intake of antidepressants, and alteration in electrolyte levels in brain cancer patients (BC) and in local population, who were taking frozen food or canned food in moderation. In brain cancer patients, depression impacts in first 8-10 months of diagnosis (Rooney *et al.*

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2011) and antidepressants are suggested as a first-line medicines. The intake of antidepressant drugs is also associated with an increased risk of dementia and cognitive abnormalities (de Gage *et al.* 2012). A positive association was found between the intake of the first generation-antidepressants and low levels of sodium in hospitalized patients (Falhammar *et al.* 2019). Mirza & Jenkins (2004) reported 34% incidence rate of depression and anxiety in Pakistan. Gadit & Mugford (2007) reported that Lahore city has the highest prevalence of depression (53.4%), in comparison with Quetta (43.9%) and Karachi (35.7%). Siddiqui *et al.* (2018) reported the prevalence of dementia as 63% of total cases of Alzheimer's disease, followed by 24% and 17% for Lewy Body Dementia and vascular dementia, respectively.

MATERIALS AND METHODS

Study design and study population

A case-control epidemiological study was conducted in the year 2018 to find the prevalence of dementia, depression, intake of antidepressants and alteration in electrolyte levels in brain cancer patients (BC; n=70) and in local population (CG; n=130) who were taking frozen food or canned food. Pakistani brain cancer patients were targeted in this study as subjects from Jinnah Hospital, Lahore and Shaikh Zayed Hospital, Lahore. Pakistani healthy volunteers with matched socioeconomic status as control group individuals from urban, rural or suburban areas of Lahore were randomly included.

Background & clinical information

Background information was gathered from both groups on pre-designed Proforma with informed consents. The participants with informed consents were interviewed by the neurologist and the existence of depressive illnesses and dementia were assessed by using a reliable self-administered Proforma. The depressed brain cancer patients were taking Fluoxetine 20mg (once daily) & Escitalopram 10mg (once daily) from group SSRI and Amitriptyline 50mg (once at bedtime) & Nortriptyline 50 mg (once at bedtime) from group TCA. Very few patients were taking Selegiline 10mg from MAOI group.

Dietary habits related to frozen food intake

The dietary pattern was assessed by using a comprehensive food intake frequency questionnaire, incorporating a list of most commonly eaten processed food items, including fridge items or frozen food (meat, chips, cheese, etc.) and canned food (fruits, beans and vegetables, etc.). All participants were questioned to indicate which food items had been the part of their diet and how often they had consumed these items over the last five years.

Blood sampling and measurements of electrolytes

A blood sample of 2ml from each individual was collected after taking written informed consent. The

samples were obtained in serum separating tubes and were sent to laboratory immediately after its collection to perform serum electrolytes test. The measurement of serum sodium levels in mmol/l and potassium mmol/l were measured from Elabscience kits (E-BC-K207) and (E-BC-K279) respectively. Electrolytes mean values (sodium & potassium) were calculated for all normal values which were found within the normal range, all values which were below the normal range and all values which were found above the normal range in both groups (i.e., BC and CG).

STATISTICAL ANALYSIS

The *Chi Square tests* were used to determine whether there is an association between each mentioned categorical variables in both groups (BC & CG). The *Odds Ratio (OR)* and *Relative Risks (RR)* were calculated of having a specific occurrence or condition (e.g., dementia, depression, intake of antidepressants and suicidal thoughts) in brain cancer patients vs. controls. *Shapiro-Wilk (W)* test was applied to determine the normalized or non-normalized distribution in each serum electrolytes parameter. *Mann Whitney (U)* test was applied to compare the above mentioned (electrolytes) parameters in both groups and identified significant results. A p-value of less than 0.050 was considered significant.

RESULTS

Background, clinical and surgical information

Table 1 describes the background information of brain cancer patients and control group individuals. No family history of cancer was found in majority of brain cancer patients and in controls. Craniotomy (gross-total resection) procedure was done in 67 (95.71%) patients and VP-shunt was done in 3 (4.23%) patients.

Assessment of dietary habits, depression and electrolytes' mean values

The majority of patients (54; 76.06%) and CG people (95; 73.08%) were taking canned food in moderation. The 16 (22.85%) patients and 35 (26.92%) CG individuals were taking canned food frequently. The majority of patients (49; 69.01%) and CG people (65; 50%) were taking frozen food in moderation. The 21 (30%) patients and 65 (50%) CG individuals were taking frozen food frequently. Frozen food in the form of meat, was found most common in both groups as compared to other frozen food. Dementia was present in the majority of patients (66; 94.28%), and there was no case of dementia in the CG. The 29 (40.85%) patients were diagnosed with depression and only 6 (4.62%) CG people were with depression symptoms. Most of the patients (63; 87.50%) and CG individuals (127; 97.69%) were not taking antidepressants. Very few patients (2; 2.82%) and controls (4;

Table 1: Background information of brain tumor patients and control group

Parameters	Brain Tumor Patients (n=70)			Control Group (n=130)		
	Sub Categories	No of Patients	Percentage Prevalence (%)	Sub Categories	No of Individuals	Percentage Prevalence (%)
Locality	Rural	15	21.13	Rural	25	19.23
	Urban	22	31.42	Urban	55	43.30
	Suburban	33	47.14	Suburban	50	36.46
Age Group	8-32 years	28	40	8-32 years	45	64.28
	33-57 years	29	41.42	33-57 years	60	85.71
	58-82 years	13	18.57	58-82 years	25	35.71
Gender	Male	37	52.11	Males	77	59.23
	Female	33	47.14	Females	53	75.71
Socioeconomic Status	Poor	45	64.28	Poor	33	25.38
	Middle Class	25	35.71	Middle Class	77	59.23
	Upper Class	None	0	Upper Class	20	15.38
Education	Illiterate	15	21.42	Illiterate	15	11.53
	Primary	9	12.68	Primary	25	19.23
	Middle	9	12.68	Middle	20	15.38
	Matric	14	20	Matric	20	15.38
	Intermediate	9	12.68	Intermediate	20	15.38
	Graduate	12	16.90	Graduate	15	11.53
	Post Graduate	2	2.85	Post Graduate	15	11.53
Occupation	Farmers	5	7.14	Farmers	7	5.38
	Field Workers	12	17.14	Field Workers	20	15.38
	Shopkeepers	8	11.42	Shopkeepers	20	15.38
	Housewives	30	42.85	Housewives	18	13.84
	Students	6	8.57	Students	25	19.23
	Teachers	5	7.14	Teachers	20	15.38
	Office Workers	4	5.71	Office Workers	20	15.38

Table 2: Mean values of electrolytes in brain tumor patients and control group

Parameters	Brain Tumor Patients (n=70)				Control Group (n=130)		
	Normal Range	Normal Values (n*, PP%**)	Above Range (n*, PP%**)	Below Range (n*, PP%**)	Normal Values (n*, PP%**)	Above Range (n*, PP%**)	Below Range (n*, PP%**)
Sodium (mmol/l)	135-147	139.4 (42, 60%)	151.6 (5, 7.04%)	130.57 (23, 32.39%)	138.162 (68, 53.13%)	151.6 (5, 3.91%)	129.236 (55, 42.97%)
Potassium (mmol/l)	3.5-5.4	4.03 (59, 84.51%)	6.3 (1, 1.41%)	3.17 (10, 14.08%)	4.282 (81, 62.31%)	6.391 (34, 26.2%)	3.06 (15, 11.54%)

*n=number of individuals/patients; *PP%=percentage prevalence

3.08%) were having suicidal thoughts. There was more occurrence of dementia (41%) and depression (6%) in patients as compared to CG. 10% patients and 2% controls were taking antidepressants. Table 2 describes the Electrolytes of Brain Tumor Patients and control group. 32% patients were having low levels of sodium and 43% were having low levels of potassium. High levels of potassium (26%) were found in CG.

Chi-Square tests

Table 3 shows an association between the occurrence of dementia, depression, suicidal thoughts and intake of antidepressants in groups: brain cancer patients (BC) and healthy individuals (CG). A significant association ($p < 0.050$) was found in occurrence of depression ($p = 0.00001$) and intake of anti-depressants ($p = 0.0185$) between brain cancer patients and control group individuals. The two groups (BC and CG) were significantly different ($p < 0.000001$) relative to type of

frozen food intake ($p = 0.0102$) and frozen food intake (Frequent/Moderate) ($p = 0.0093$). Odds Ratio (OR) and Relative Risks (RR): Table 3 shows the values of odds ratios and relative risks for specific parameter(s) in BC vs. CG. Odds ratios were values greater than one (17.4, 14.2 & 4.6 respectively) and significant in the occurrence of dementia, depression and intake of anti-depressants at p-values: < 0.0001 , < 0.001 and 0.0302 . The occurrences of depression and intake of anti-depressants were also significant in chi-square test between both groups. Therefore, higher odds of outcome ($OR > 1$) were reported in dementia, depression and intake of anti-depressants for BC vs. CG. Similarly, the relative risks were greater than one (2.9, 3.2 & 2 respectively) and significant in the occurrence of dementia, depression and intake of anti-depressants at p-values: < 0.0001 , < 0.0001 and 0.0014 . There existed a 194% increased risk of dementia, 227% increased risk of depression and 109% increased risk of intake of anti-depressants in brain cancer patients as

Table 3: Association between occurrence of dementia, depression, suicidal thoughts and intake of antidepressants

Groups	Occurrence of dementia		Total	Chi Square	p-value	Odds Ratio (OR)	Relative Risk (RR)
	Yes	No					
Brain Tumor Patients (n=70)	4	66	70	Chi-square cannot be calculated	-	17.400>1; 95%CI: 0.9231- p=0.0566*	2.9403>1; (194% Increased Risk) 95%CI: 2.4205 to 3.571 p<0.0001*
Controls (n=130)	0	130	130				
Total	4	197	201				
	Occurrence of depression						
Brain Tumor Patients (n=70)	29	41	70	41.9132	0.00001*	14.2698>1; 95% CI: 5.5401- 36.7556 p<0.0001*	3.2748>1; (227.48% Increased Risk) 95% CI: 2.4219- 4.4282 p<0.0001*
Controls (n=130)	6	124	130				
Total	35	166	201				
	Suicidal thoughts						
Brain Tumor Patients (n=70)	2	68	70	0.0107	0.917533	0.9130<1; 95%CI: 0.1631- 5.1122 p=0.9176	0.9420<1; 95% CI: 0.2991-2.9674 p=0.9187
Controls (n=130)	4	126	130				
Total	6	195	201				
	Intake of antidepressant						
Brain Tumor Patients (n=70)	7	63	70	5.5389	0.018598	4.6302>1 95%CI: 1.1585- 18.5061 p=0.0302*	2.0891>1;(108.91 % Increased Risk) 95% CI: 1.3290- 3.2838 p=0.0014*
Controls (n=130)	3	127	130				
Total	10	191	201				

*Highly significant p value

Table 4: Association between canned food intake & frozen food intake and groups: brain tumor patients (BP) and healthy individuals (CG)

Groups	Intake of Canned Food		Total	Chi Square	p-value
	Frequent	Moderate			
Brain Tumor Patients (n=70)	16	54	70	0.2126	0.644773
Controls (n=130)	35	95	130		
Total	52	149	201		
	Frozen Food Intake				
	Frequent	Moderate			
Brain Tumor Patients (n=70)	21	49	70	6.7628	0.009308*
Controls (n=130)	65	65	130		
Total	87	114	201		

*Highly significant p value

compared to controls. *Shapiro-Wilk (W) Test:* As determined from Shapiro-Wilk (W) test, the data was distributed non-normalized in the values of serum electrolyte parameters, i.e., sodium levels, and potassium at p values: 0.000<0.050. *Mann-Whitney (U) Test:* As per Mann Whitney test, potassium levels (Z score: 1.2659; p value: 0.00001) and sodium levels score: -2.44183; p value: 0.01468) were found at significant difference in brain cancer patients and control group. Table 4 describes chi-square test for dietary habits. There is a significant association in frozen food intake two between groups.

DISCUSSION

Frozen food and canned food chemicals contain neurotoxins which disturb electrolyte levels. It was reported that, depression, antidepressant use, history of

seizures or surgical treatments were associated with suicidal ideation (Brinkman *et al.* 2013). Akbaraly *et al.* (2009) found a positive correlation between canned food intake and pathogenesis of depression (Hilimire *et al.* 2015). A strong positive correlation was found between excessive consumption of packed fruit juices/soda drinks and poor mental performance (Pabayo *et al.* 2016). The prenatal and postnatal dietary patterns high in packed food had resulted in impaired mental performance (Barker *et al.* 2013) and emotional difficulties (Mesirow *et al.* 2016). Sodium and potassium salts of nitrate and nitrite are widely used to cure meat products, which are carcinogens and can induce brain cancer (Dietrich *et al.* 2005). The frequency of depression in clinically diagnosed Glioma patients was reported as 15% (Rooney *et al.* 2011). A long-term intake of antidepressants has also been linked with an increased neurogenesis

(Dranovsky & Hen, 2006). Lower levels of sodium were common in both groups. Frozen preserved food contains altered levels of sodium and potassium and nutritional deficiency or toxicity can be occurred. Leshem (2011) investigated the association of low dietary sodium with depression and anxiety. Hyponatremia occurs from an osmotic swelling of brain cells, and symptoms such as lethargy, headaches, drowsiness, confusion, restlessness, irritability, manic behavior, muscle weakness, disorientation and behavioral changes can be observed (Ayus *et al.* 1992). Low levels of potassium have also seen in depressed patients (Coppen *et al.* 1966). A chronic hyponatremia induces mild cognition impairment (MCI) (Renneboog *et al.* 2006), which in turn leads to an increased risk of dementia progression (Cooper *et al.* 2015). Ohsawa *et al.* (1992) determined that 10.5% psychiatric patients had hyponatremia. It had been observed that 50-80% brain cancer patients can be depressed (Arnold *et al.* 2008). In high-grade Glioma patients, the depression was found in the preoperative and postoperative periods (Lipofsky *et al.* 2004). Frozen or packed/canned food contain varied levels of sodium, potassium levels in the form of different chemicals, and hence, a nutrient varied food can develop malnutrition states, which can further impact neurotransmitters. The occurrence of hyponatremia was occurred in 15% in the general community (Tisdall *et al.* 2006). Hyponatremia can disturb different neurological conditions. An association was found between depression managing drugs, such as, mirtazapine, serotonin reuptake inhibitors and serotonin-modulating antidepressants, with the incidence of hyponatremia (Mazhar *et al.* 2019). 26% of our control population was found having high levels of potassium. Higher potassium consumption is linked with higher odds of cognitive decline (Nowak *et al.* 2018). Vintimilla *et al.* (2018) reported that increased serum potassium levels predicted a mild cognitive impairment (MCI).

CONCLUSION

Electrolyte abnormalities from the food chemicals can disturb the activity of neurotransmitters, and can lead to mental disorders. There is a need to conduct larger studies to affirm facts. Further, there is a strong need to reduce dependability on the frozen food. Compliance with Ethical Standards Statement: Informed consents were obtained from all patients conformed to collaborative hospitals' ethical standards. The author reports no conflict of interest.

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