RESEARCH ARTICLE

NEUROLOGICAL COMPLICATIONS IN DIABETIC KETOACIDOSIS – BEFORE AND AFTER INSULIN THERAPY

Manmohan K Pandey[1], Purnima Mittra[1], Jitendra Doneria[2], Pradeep Maheshwari[2]
[1] Rohilkhand Medical College, Bareilly, UP, India
[2] SN Medical College, Agra, UP, India

Correspondence to: Manmohan K Pandey (drmkp12@yahoo.com)

DOI: 10.5455/ijmsph.2013.2.88-93 **Received Date: 01.10.2012** **Accepted Date: 01.10.2012**

ABSTRACT

Background: Neurological complications in DKA may present before, during and after the therapy. Present study was designed to evaluate neurological complication in DKA and effects of insulin therapy.

Aims & Objective: To compare neurological complications of DKA before and after insulin therapy.

Material and Methods: This was Cross-Sectional Study with sample size of 40. 40 cases of diabetes mellitus in DKA were given standard treatment with intravenous insulin infusion and fluids. Patients were compared with the symptoms and signs of DKA before and 12 hours of insulin therapy. Result were analyzed with Graph Pad Software with paired t-test and discussed in terms of p-value.

Results: The general symptoms like pain in abdomen, thirst, nausea and vomiting and general signs of DKA like tachycardia, hypotension dry mucous membrane, dehydration and Kussmaul's respiration showed clinically significant improvement and statistically very significant with p-value less than 0.05 after insulin infusion therapy. The CNS symptoms like headache, altered mentation, unconsciousness and abnormal verbal/motor response to pain increased after 12 hours of insulin infusion therapy and intravenous fluids and results were statistically significant with p-value 0.0221 and CNS signs of DKA i.e. bradycardia, extensor planter response, papilledema and third cranial nerve palsy showed clinically significant results but statistically not significant with p-value 0.0911 after insulin infusion therapy.

Conclusion: CNS manifestation of DKA may aggravate symptoms and signs with insulin infusion therapy. Patient should be monitored for CNS manifestations during therapy along with oxygen saturation, blood pressure, hydration and other vital parameters.

KEY-WORDS: Diabetic Ketoacidosis; Central Nervous System; Cerebral Edema; Diabetes Mellitus

Introduction

DKA is a syndrome characterized by hyperglycaemia, ketosis, and acidosis. It occurs as the result of a relative or absolute insulin deficiency and an excess of insulin counter-regulatory hormones (ICRH).[1] This hormonal imbalance promotes glycolysis, glycogenolysis and inhibits peripheral utilization of glucose by muscles and adipose tissues resulting in accelerated breakdown of proteins and lipolysis. This results in hyperglycaemia, increased free fatty acids, glycerol, amino acids and lactate. The β -oxidation of free fatty acids in the liver results in increased production of ketone bodies namely β-hydroxy-butyrate and acetone leading to hyperketonemia causing acidosis and increased anion gap. Insulin deficiency leads to increased glycogenolysis and gluconeogenesis and decreased glycolysis. Hyperglycaemia and heavy glycosuria lead to osmotic diuresis, water and electrolyte loss causing severe dehydration, hypotension and shock.[2]

Before the discovery of insulin in 1922, the mortality due to DKA was virtually 100%.[3] With the discovery of insulin, antibiotics, intravenous potassium replacement and use of nor-epinephrine for blood pressure support[4] mortality rates ranging from 2.5% to 9% among patients admitted with DKA in more recent studies.[5-7]

Cerebral complications of DKA (including much less frequent cerebral arterial infarctions, venous sinus thrombosis, and central nervous system infections) are the most common cause of diabetic-related death of young diabetic patients[8], accounting for 31% of deaths associated with DKA and 20% of all diabetic deaths, having surpassed aspiration, electrolyte imbalance, myocardial infarction, etc.

Cerebral edema is a rare but fatal complication of DKA that primarily occurs in children. In the largest reported series, 95% of cases occurred in patients younger than 20 years, with one third occurring in patients younger than 5 years.[9] It occurs in children who seem to be metabolically returning to normal, generally 3-12 hours after the initiation of therapy.[10-12] Subclinical cerebral edema is common if not universal during treatment of DKA both in adults[13,14] and children.[11] The incidence of cerebral edema in children with DKA is between 0.7% and 1%.[15-17] It is more common in patients with newly diagnosed diabetes[15] and is the most common cause of death in young children with diabetes.[18] The mortality rate according to different series has varied widely, with reports between 24% and 90%.[17,19] The clinical presentation of cerebral edema is characterized by deterioration in the level of consciousness, with lethargy, decrease in arousal and headache.[1,15] The timing of the development of cerebral edema is variable, with most cases occurring 4 to 12 hours after starting treatment. Several case reports showed presence of cerebral edema before the initiation of therapy.[19] A method of clinical diagnosis based on bedside evaluation of neurological state in DKA have been developed.[20]

Brain edema does not occur if hyperglycaemia is corrected with even massive quantities of hypotonic[27] or isotonic[28] fluids; if however hyperglycaemia is treated with a combination of fluids and insulin, the brain accumulates further cations and other osmotically active substances, and brain edema occurs. Studies suggested that cerebral edema occurs only after the initiation of therapy and insulin therapy has been associated with cerebral edema in this setting.[3] Possible contributing factors of DKA include hypoxia, the osmotically driven movement of water into the CNS when plasma osmolality declines too rapidly during the treatment of DKA, and the direct effect of insulin on the plasma membrane of brain cells, which may promote cellular oedema.[1,15,19] This study was done to assess cerebral complication of DKA and effect of insulin therapy on the CNS manifestation of DKA as few studies have been done on humans to understand pathophysiology and symptomatology. Hence, the study was planned for neurological assessment of patients before and after insulin therapy in DKA.

Materials and Methods

This study was done in tertiary care centre of North India with approval of Medical College Ethical Committee and was done after taking patient or their relative consent. 40 cases with different time duration of diabetes mellitus in DKA were included in the study. Patients with diagnosis of diabetic mellitus with symptoms of headache, vomiting blurring of vision, pain in abdomen and lab supported diagnosis of DKA were included in the study while patients with starvation ketosis, alcoholic ketoacidosis, lactic acidosis, salicylate intoxication, methanol /ethylene glycol intoxication, chronic renal failure, pregnancy and pseudo-ketosis were excluded.

Patients were subjected to detail clinical examination and assessed for age, height /weight, BMI and investigated for blood sugar (fasting, random and post-prandial), urine sugar and ketone-bodies, serum ketones, creatinine, urea, sodium, potassium; arterial blood gas(ABG) analysis, urine and blood cultures, total leukocyte and differential count, chest X ray and ECG.

Cases with signs or symptoms and investigations suggestive of diabetic ketoacidosis were given intensive treatment of DKA with intravenous insulin and fluid infusion. Symptoms and signs were compared before and after twelve hours of starting insulin infusion.

Results

Maximum numbers of cases were in age group 40-50 (Table 1) and maximum number of patients had diabetes for 6-10 years of duration (Table 2). Forty patients were evaluated for signs and symptoms of diabetic ketoacidosis at the time of presentation and after 12 hours of insulin therapy.

The general symptoms of DKA like pain in abdomen (↓68%→30%), nausea and vomiting (↓87%→10%), thirst (↓80%→7.5%) showed clinically significant improvement and statistically very significant with p-value 0.0025 after insulin infusion therapy (Table 3). The general signs of DKA like tachycardia, hypotension, dry mucous

membrane, dehydration and Kussmaul's respiration showed clinical improvement and statistically extremely significant with p-value 0.0001 after insulin infusion therapy (Table 4).

Table-1: Age and Sex Distribution

Age (in years)	Male	Female	Total (%)
Up to 30	2	1	3 (8.00)
30 – 40	3	2	5 (12.00)
40– 50	10	6	16 (40.00)
50 – 60	8	5	13 (32.00)
>60	1	2	3 (8.00)
Total	24	16	40 (100.00)

Table-2: Duration of Diabetes Mellitus

Duration (in years)	Male	Female	Total (%)
0–5	4	2	6 (15.00)
6 –10	14	11	25 (62.50)
11– 15	3	2	5 (12.50)
16 –20	3	1	4 (10.00)
Total	24	16	40 (100.00)

Table-3: General Symptoms of DKA – Before & After Insulin Therapy

General Symptoms	Before Insulin Therapy (%)	After Insulin Therapy (%)
Nausea/Vomiting	35 (87.50)	4 (10.00)
Thirst	32 (80.00)	3 (7.50)
Pain in abdomen	27 (67.50)	12 (30.00)

t-value – 6.7902; p-value – 0.0025 (very significant)

Table-4: General Signs of DKA – Before and After Insulin Therapy

General Signs	Before Insulin Therapy (%)	After Insulin Therapy (%)
Tachycardia	32 (80.00)	10 (25.00)
Hypotension	28 (70.00)	8 (20.00)
Dry mucous membrane	35 (87.50)	12 (30.00)
Dehydration	34 (85.00)	10 (25.00)
Kussmaul Respiration	24 (60.00)	4 (10.00)

t-value – 8.8998; p-value <0.0001 (extremely significant)

Table-5: Neurological Symptoms of DKA – Before and After Insulin Therapy

Neurological Symptoms	Before Insulin Therapy (%)	After Insulin Therapy (%)
Altered mentation	10 (25.00)	12 (30.00)
Unconsciousness	3 (7.50)	4 (10.00)
Abnormal verbal/motor response to pain	2 (5.00)	3 (7.50)
Headache	4 (10.00)	12 (30.00)

t-value – 4.3727; p-value – 0.0221 (significant)

Table-6: Neurological Signs of DKA – Before and After Insulin Therapy

Neurological Signs	Before Insulin Therapy (%)	After Insulin Therapy (%)
Bradycardia	2 (5.00)	7 (17.50)
Extensor planter	3 (7.50)	10 (25.00)
Papilledema	5 (12.50)	7 (17.50)
Cranial-nerve palsy (III)	1 (2.50)	2 (5.00)

t-value – 2.0105; p-value – 0.0911 (not significant)

CNS symptoms like headache (10%→30%), altered mentation (25%→30%), unconsciousness (8%→10%) and abnormal verbal/motor response to pain (5%→8%) increases after 12 hours of insulin infusion therapy and intravenous fluids and results were statistically significant with p-value 0.0221 after insulin infusion therapy (Table 5).

CNS signs of DKA i.e. bradycardia (5%→18%), extensor planter response (8%→25%), papilledema (12%→18%), third cranial nerve palsy (3%→5%) shows clinically but not statistically significant results (p-value 0.0911) after insulin infusion therapy (Table 6).

Discussion

Type 2 DM constitute about 98 % of DM in India.[24] Overall 6-8% of diabetic undergo in DKA in their lifetime. Type 1 DM has a risk of 20% in life time.[2] This study also have age group suggestive of maximum numbers having DKA are type 2 DM. Several studies reported that the average age of patients admitted for DKA was 40 to 50 years[5,25], but that the risk decreased with age[27]. This study have data supporting previous studies as maximum patients are in the age group of 40-50 years. The male to female ratio is 1.5/1 in the study. Some studies have reported a female predominance[5,7,26,27], possibly because young women were more likely to have repeated episodes of DKA[7,28].

DKA is an emergency condition caused by a severe lack of insulin that results in high blood glucose levels and an accumulation of acidic ketones in the blood.[29,30] DKA-CE is a rare but potentially devastating complication in children that occurs with in the first day of therapy.[31-33] The mortality associated with DKA-CE is estimated at 21–25% and significant neurologic morbidity at 10–26%.[31] The cause of DKA-CE is a source of considerable debate.[29,34,35] The mechanisms proposed to elicit DKA-CE include increases in hydrostatic and/or decreases in osmotic pressure, increases in blood brain barrier permeability, loss of cerebral vascular auto-regulation and subsequent changes in cerebral blood flow, production of intracellular osmoles in brain cells, and/or intracranial acidosis. Studies have linked newly diagnosed diabetes, young age,

low blood CO2, high blood urea nitrogen and administration of bicarbonate to the development of DKA-CE.[33,36,37] These epidemiologic studies may identify children at risk for developing of DKA-CE, animal studies will provide insight into the cellular mechanisms contributing to DKA-CE. Insulin-deficient juvenile mice develop biochemical changes that are similar to those of DKA in children. Increased BWC (Brain Water Content) was observed only in DKA mice that received combined insulin and bicarbonate therapy, suggesting that rapid systemic alkalinisation in the presence of insulin may contribute to DKA-CE.[38] The DKA-CE observed with combined bicarbonate and insulin therapy reflects both overhydration of the cerebral parenchyma[31] and direct cellular swelling[35]. Indeed, edema was evident in both perineuronal and perivascular spaces. These neuropathological changes were most prevalent in the basal ganglia, a finding that correlates with imaging studies on children with DKA-CE.[39,40] The patients who survive after DKA, 20 to 40 % suffer from serious and permanent neurological disability including motor deficits, visual impairment, seizure disorder, learning disability and speech disturbance.[41,42] Cerebral edema complicating DKA is a paediatric problem and is almost unknown in adults.[41] Cerebral edema typically occurs 4-12 hours after treatment is activated.[43,44] However, it may develop any time during treatment for DKA and can even be present before treatment has begun.[45-49] Cerebral edema is primarily a clinical diagnosis and should be suspected when there is an unexpected deterioration in neurological status after initial improvement or persistence of a comatose state without an obvious cause. Warning signs include lethargy, decrease in arousal, headache, vomiting, bradycardia and hypertension.[41] Neurological deterioration may be rapid, with seizures, incontinence, pupillary changes and respiratory arrest. Progression may be so rapid that papilledema may not be found. Once clinical symptoms other than lethargy and behavioural changes occur, mortality is high (>70%), with only 7-14% of the patients recovering without permanent morbidity.[9] Rosenbloom reported post-mortem studies on 24 of his series of 69 patients.[41] Cerebral oedema was universal and brain stem herniation was present in almost all. 10% of episodes of clinical cerebral oedema are due to localized basilar oedema, and another 8 to 10% are as a result of infection, thrombosis or haemorrhage. Two population based studies of demographic factors associated with cerebral oedema in DKA have been reported in recent years.[42,49] In a prospective record of all cases of DKA in the UK over a 3-year period between 1995 and 1998, Edge, et al. reported 34 cases of well documented cerebral oedema from among 2940 episodes of DKA (0.68% or 6.8 per 1000 cases).[42] A further 26 children with unexplained deterioration in consciousness and two deaths in children suspected to have had cerebral oedema before admission to hospital. The Canadian prospective population based study reported a similar frequency of 5.1 per 1000 cases of DKA.[49] Higher frequencies have been reported from centres which cares the sickest children, for example 13.2% in a report from a paediatric intensive care unit of a tertiary care hospital in India.[50] Edge, et al. reported higher frequency of cerebral oedema in new onset type 1 DM (11.9 per 1000 cases) compared to children with known DM (3.8 per 1000 cases).[42] This association was also reported by the Canadian study[49] and other non-population based reports[41,51], and in a multicentre study from North America[43]. Association with younger age group has been noted in cases of cerebral oedema[41] though not in the recent prospective population based reports[42,49]. Bellos, et al. have reported an association with longer duration of symptoms before treatment of diabetes.[51]

Glaser et al.[39] reported lower partial pressure of carbon dioxide in 61 DKA cases with cerebral oedema in comparison with not only 184 random DKA controls but also 174 cases matched for venous pH. The association remained significant on multivariate analysis.[43] Alkali therapy, which can cause paradoxical CNS acidosis, was shown in an experimental study to produce cerebral hypoxia in dogs.[32] In the clinical study by Glaser, et al.[43], the use of bicarbonate gave a relative risk 4.2 (95% CI 1.5-12.1,$p < 0.008$) for the development of cerebral oedema. A delayed or inadequate rise in corrected serum sodium as glucose levels fall during therapy of DKA (giving rise to lower plasma osmolality) has been correlated with occurrence of cerebral oedema in a large number of studies.[43,52-55] Durr, et al.[56] showed blood glucose at onset and the rate of fall of blood glucose and osmolality with treatment to correlate positively with occurrence

and progression of asymptomatic cerebral oedema as seen by CT scan, this has not been shown to be the case in most studies of symptomatic cerebral oedema.[31,38,39,41,43,51] The use of hypoosmolal (0.45%) saline was found to be associated with cerebral oedema by Harris, et al.[53] Severity of acidosis was correlated significantly in asymptomatic cerebral oedema by Durr, et al.[56] as described above as well as the Canadian population based study[49] but not in other clinical symptomatic cerebral oedema reports[41,43]. Concomitant with the activation of the Na+-H+ exchanger, there occur other complex alterations such as activation of other pumps which induce a loss of other anions and cations from the brain cell. The PET scanning and MR spectroscopy are non-invasive tools which can detect earliest changes of cerebral oedema in DKA.[42]

In Rosenbloom's analysis[41] of 69 patients, more than 50% of patients treated for cerebral oedema before the occurrence of respiratory arrest survived completely normal while only 6.5% of those treated after respiratory arrest. These descriptions belies the popularly held belief that mortality is universal in cerebral oedema, and indicate for vigorous efforts to prevent DKA, prevent cerebral oedema, recognize and treat it early. In conclusion, the CNS manifestation of DKA may aggravate with insulin infusion therapy. Patient should be monitored for CNS manifestations during therapy along with oxygen saturation, blood pressure, hydration and other vital parameters and urgent management is needed.

Conclusion

CNS manifestation of DKA may aggravate symptoms and signs with insulin infusion therapy. Patient should be monitored for CNS manifestations during therapy along with oxygen saturation, blood pressure, hydration and other vital parameters.

Cerebral edema is a complication of DKA in both children as well as adults. This should be monitored before, during and after the DKA management and treated to avoid fatal complications and prevent persistent neurological deficits.

References

1. Magee MF, Bankim AB. Management of decompensated diabetes. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. Crit Care Clin 2001;17(1):75–106.
2. Ramachandran A. Acute Complications of Diabetes Mellitus. API Text Book of Medicine .8th EDN;1056-1057
3. Kitabchi AE. et al. Diabetic ketoacidosis and the hyperglycaemic hyperosmolar nonketotic state. Joslin's diabetes mellitus, Lippincott Williams & Wilkins, 1994:739–765.
4. Skillman T, Wilson R, Knowles H. Mortality of patients with diabetic acidosis in a large city hospital. Diabetes 1958;7:109–113.
5. Faich G, Fishbein H, Ellis S. The epidemiology of diabetic acidosis: a population-based study. Am J Epidemiol 1983;117:551–558.
6. White N. Diabetic ketoacidosis in children. Endocrinol Metab Clin North Am 2001;29:657–682.
7. Ellemann K. et al. Epidemiology and treatment of diabetic ketoacidosis in community population. Diabetes Care 1984;7:528–532.
8. Scibilia J, Finegold D, Dorman J, Becker D, Drash A. Why do children with diabetes die? Acta Endocrinol Suppl. 1986; 279:326-33.
9. Rosenbloom AL. Intracerebral crisis during the treatment of diabetic ketoacidosis. Diabetes Care 1990;13:22–33.
10. Bratton SL, Krane EJ. Diabetic Ketoacidosis: Pathophysiology, Management and Complications. J Intensive Care Med. 1992; 7:199-211.
11. Krane EJ. Diabetic ketoacidosis. Biochemistry, physiology, treatment, and prevention. Pediatr Clin North Am. 1987; 34:935-60.
12. Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JI. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. N Engl J Med. 1985; 312:1147-51.
13. Clements RS, Blumenthal SA, Morrison AD, Winegard AI. Increased cerebrospinal fluid pressure during therapy for diabetic acidosis. Trans Assoc Am Physicians. 1971; 84:102-12.
14. Fein IA, Rachow EC, Sprung CL, Grodman R. Relation of colloid osmotic pressure to arterial hypoxemia and cerebral oedema during crystalloid volume loading of patients with diabetic ketoacidosis. Ann Intern Med. 1982; 96:570-5.
15. Kitabchi AE. et al. American Diabetes Association Hyperglycemic crises in diabetes. Diabetes Care 2004;27(Suppl 1):S94–102.
16. Glaser N. et al. Risk factors for cerebral oedema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001;344(4):264–9.
17. Edge JA, et al. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child 2001;85:16–22.
18. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes. Arch Dis Child 1999;81:318–23.
19. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? Diabetes Metab Res Rev 2000;16:316–24.

20. Muir AB, Quisling RG, Yang MC, Rosenbloom AL. Cerebral Oedema in Childhood Diabetic Ketoacidosis:Natural history, radiographic findings, and early identification. Diabetes Care 2004: 27: 1541–1546.
21. Tornheim PA. Regional localization of cerebral oedema following fluid and insulin therapy in streptozotocin-diabetic rats. Diabetes. 1981; 30:762-6.
22. Arieff AI, Kleeman CR. Studies on mechanisms of cerebral oedema in diabetic comas. Effects of hyperglycemia and rapid lowering of plasma glucose in normal rabbits. J Clin Invest. 1973; 52:571-83.
23. Arieff AI. Cerebral oedema complicating nonketotic hyperosmolar coma. Miner Electrolyte Metab. 1986; 12:383-9.
24. Maji D. Pathogenesis of Diabetes Mellitus. API Text Book of Medicine .8th EDN;1056-1057.
25. Kreisberg R. Diabetic ketoacidosis: Diabetes mellitus: theory and practice, 4th ed. New York: Elsevier Science, 1990:591–603.
26. Javor K et al. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. Diabetes Care 1997;20: 349–354.
27. Johnson D, Palumbo P, Chu C. Diabetic ketoacidosis in a community-based population. Mayo Clin Proc 1980;55:83–88.
28. DeFronzo R, Matsuda M, Barrett E. Diabetic ketoacidosis: a combined metabolic-nephrologic approach to therapy. Diabetes Rev 1984;2:209–238.
29. Rosenbloom AL et al.Therapeutic controversy: prevention and treatment of diabetes in children. J Clin Endocrinol Metab2000; 85:494–522.
30. Chiasson JL et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. CMAJ 2003;168:859–866.
31. Dunger DB. Et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents.Arch Dis Child 2004;89:188–194.
32. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral oedema in pediatric diabetic ketoacidosis.J Pediatr2005; 146:688–692
33. Glaser N et al. Risk factors for cerebral oedema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001;344: 264–269.
34. Carlotti AP, Bohn D, Halperin ML. Importance of timing of risk factors for cerebral oedema during therapy for diabetic ketoacidosis. Arch Dis Child 2003;88:170–173
35. Bohn D, Daneman D. Diabetic ketoacidosis and cerebral oedema. Curr Opin Pediatr2002; 14:287–291
36. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? Diabetes Metab Res Rev 2000;16:316–324
37. Marcin JP et al. Factors associated withadverse outcomes in children with diabetic ketoacidosis-related cerebral edema.J Pediatr 141:793–797
38. Keeley L.et al. Combined Insulin and Bicarbonate Therapy Elicits Cerebral Edema in a Juvenile Mouse Model of Diabetic Ketoacidosis Pediatr Res 61: 301–306, 2007)
39. Glaser NS et al Mechanism of cerebral oedema in children with diabetic ketoacidosis. J Pediatr 145:164–171
40. Muir AB, Quisling RG, Yang MC, Rosenbloom AL. Cerebral oedema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. Diabetes Care2004; 27:1541–15
41. Rosenbloom AL. Intracerebral crisis during treatment of diabetic ketoacidosis. Diabetes Care 1990; 13: 22-31.
42. Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child 2001; 85: 16-22.
43. Glaser N. et al. Risk factors for cerebral oedema in children with diabetic ketoacidosis. N Engl J Med 2001; 344: 264-269.
44. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: Are we any nearer finding a cause? Diabetes Metab Res Rev 2000; 16: 316-324.
45. Hoffman WH, Steinhart CM, el Gammal T, Steele S, Cuadrado AR, Morse PK. Cranial CT in children and adolescents with diabetic ketoacidosis. Am J Neuroradiol 1988; 9: 733-739.
46. Deeb L. Development of fatal cerebral oedema during outpatient therapy for diabetic ketoacidosis.Pract Diab 1989; 6: 212-213.
47. Glasgow AM. Devastating cerebral oedema in diabetic ketoacidosis before therapy. Diabetes Care 1991; 14: 77-78.
48. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990-96. Arch Dis Child 1999; 81: 318-323.
49. Lawrence SE, Cummings EA, Gaboury I., Daneman MB. Population-based study of incidence and risk factors for cerebral oedema in pediatric diabetic ketoacidosis. J Pediatr 2005;146: 688-692.
50. Jayashree M, Singhi S. Diabetic ketoacidosis: Predictors of outcome in a pediatric intensive care unit of a developing country. Pediatr Crit Care Med 2004; 5: 427-433.
51. Bello FA, Sotos JF. Cerebral edema in diabetic ketoacidosis in children. Lancet 1990; 336-364.
52. Carlotti APCP, Bohn D, Halperin ML. Importance of timing of risk factors for cerebral oedema during therapy for diabetic ketoacidosis. Arch Dis Child 2003; 88: 170-173.
53. Harris GD, Fiordalisi I, Harris WL, Mosovich LL, Finberg L. Minimizing the risk of brain herniation during treatment of diabetic ketoacidemia: a retrospective and prospective study. J Pediatr 1991; 118: 166-167)
54. Hale PM. et al Factors predicting cerebral oedema in young children with diabetic ketoacidosis and new onset type 1 DM. Acta Pediatr 1997; 86: 626-631.
55. Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. J Pediatr 1988; 113:10 - 14.
56. Durr JA et al. Correlates of cerebral oedema in uncontrolled IDDM. Diabetes Care 1992;41: 627-632.
57. Harris GD, Fiordalisi I. Physiologic management of diabetic ketoacidemia: A 5 year prospective pediatric experience in 231 episodes. Arch Pediatr Adol Med 1994; 148:1046-1052.

Cite this article as: Pandey MK, Mittra P, Doneria J, Maheshwari PK. Neurological complications in diabetic ketoacidosis - before and after insulin therapy. Int J Med Sci Public Health 2013; 2:88-93.
Source of Support: Nil
Conflict of interest: None declared