Original Article

How Useful is Glucose Detection in Diagnosing Cerebrospinal Fluid Leak? The Rational Use of CT and Beta-2 Transferrin Assay in Detection of Cerebrospinal Fluid Fistula

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BACKGROUND: This report describes the sensitivity and specificity of glucose detection using Glucostix test strips and computed tomography (CT) of the skull base for confirming cerebrospinal fluid (CSF) fistulae in patients with persistent rhinorrhoea or otorrhoea, and comparing them with the beta-2 transferrin assay as the gold standard for CSF detection.

METHODS: Fluid samples from the nose were collected from 18 patients with suspected CSF fistulae. The samples were assayed for beta-2 transferrin using the Western blotting and immunostaining technique. CT (5 mm axial slice) of the skull base was performed for evidence of skull base fracture. The glucose levels and Glucostix results were compared.

RESULTS: Out of the 18 samples, 15 were positive for beta-2 transferrin and the leaks were validated surgically in 10 patients. Five leaks healed spontaneously with conservative management. Glucostix tests produced three false positive results from blood and nasal mucus contaminated fluid. Glucostix failed to detect another three CSF leaks resulting from false negative tests because of low CSF glucose levels. The Glucostix glucose test was non-specific and insensitive compared with the beta-2 transferrin assay. CT failed to detect three out of the 15 beta-2 transferrin-positive leaks but there were no false positive results. CT produced six negative results, of which three were false negatives.

CONCLUSIONS: Glucose detection using Glucostix test strips is not recommended as a confirmatory test due to its lack of specificity and sensitivity. In the presence of a skull base fracture on CT and a clinical CSF leak, there is no need for a further confirmatory test. In cases where a confirmatory test is needed, the beta-2 transferrin assay is the test of choice because of its high sensitivity and specificity. [*Asian J Surg* 2004;27(1):39–42]

Introduction

A cerebrospinal fluid (CSF) leak presenting with rhinorrhoea or otorrhoea occurs when there is a fistula between the dura and the skull base. This can be due to traumatic or non-traumatic causes. Ascending bacterial infection causing meningitis or intracranial sepsis is the major concern.[1,2] Persistent rhinorrhoea or otorrhoea may indicate an unhealed fistula, which requires invasive procedures for localization and repair.[3–7] However, coincidental nasal or ear discharge or bleeding may confuse the diagnosis.

Testing for the presence of glucose in sample fluid from the nose and ear suspected to contain CSF using Glucostix test strips (Roche, Indianapolis, IN, USA) has been a traditional bedside test for the detection of CSF leaks. Nonetheless, there is dispute over its sensitivity and specificity, and it is unclear whether it is a reliable clinical tool.

CSF can leak through a bony breach at the skull base,

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which is often visible with computed tomography (CT). The development of fine-slice CT has increased the degree of confidence in diagnosing CSF leaks.

Beta-2 transferrin is a carbohydrate-free (desialated) isoform of transferrin, which is almost exclusively found in the CSF.[8–15] Beta-2 transferrin is not present in blood, nasal mucus, tears or mucosal discharge. This protein was first described by Irjala et al in 1979.[10] Intense research over the last decade has validated its characteristics and value in clinical use as a specific CSF marker.[9–13,16–19]

Beta-2 transferrin assay of the sample fluid is employed to detect the presence of CSF and to confirm an unhealed fistula. The sensitivity and specificity of Glucostix test strips and CT (5 mm axial slice) were assessed, and the results compared with those of the beta-2 transferrin assay, which was used as the gold standard.

Patients and methods

Fluid samples from the nose and ear were collected from patients presenting with rhinorrhoea and otorrhoea who were suspected of having CSF leaks. The fluid samples were tested for beta-2 transferrin by centrifugation, polyacrylamide gel electrophoresis, Western blotting, and immunostaining. At least three or four dilutions of each sample and a positive CSF control were assayed in parallel for each patient (Figure).

Glucose levels in nasal and ear discharge were measured in the biochemistry department, and Glucostix test strips (Roche) were used to test the glucose levels for comparison. CT (5 mm axial slice) of the skull base was performed in all patients to look for features of skull base fractures (fracture lines in the anterior and middle cranial fossa, fluid/blood levels over the paranasal sinus or mastoid region, or pneumocranium).

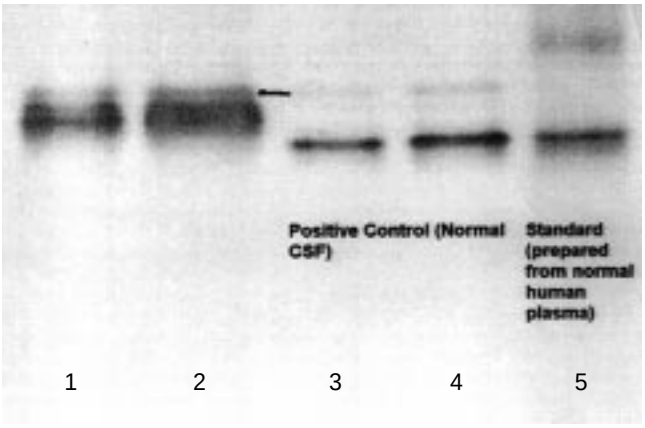

Figure. Column 1 shows the negative control (patient's serum), which has a beta-1 transferrin band only. Columns 2 and 3 show the CSF positive controls at different dilutions, which have beta-2 transferrin as well as beta-1 transferrin bands. Columns 4 and 5 show the sample fluid (blood-stained nasal discharge) at different dilutions, which have clear beta-2 transferrin bands (from the CSF) and thick bands of contaminants (from blood), confirming the CSF leak.

Results

Eighteen patients with suspected CSF leaks were studied (Table 1). Half of the leaks were caused by trauma, while non-traumatic causes accounted for the remainder. Of the 18 patients sampled, 15 were positive for beta-2 transferrin. In 10 patients, CSF fistulae were surgically validated. The leaks of five patients healed spontaneously with conservative management. Three patients were found not to have a leak. All patients were clinically well prior to the event.

Only samples from 12 of the 15 patients identified by Glucostix as having CSF leaks were actually positive for glucose; Glucostix resulted in three false positive results due to blood in the nasal discharge. Glucostix missed three CSF leaks because the CSF glucose level was lower than the detection limit of the test. The CSF glucose levels in these three samples were 2.2 to 2.8 mmol/L.

CT failed to detect three of the 15 beta-2 transferrin-positive CSF leaks (sensitivity = 0.8), but produced no false positive result (positive predicting value = 1). CT produced a total of six negative results, of which three were false negative results (i.e. CSF was leaking, specificity = 1, negative predictive value = 0.5).

By accepting the scientific basis of beta-2 transferrin as being CSF-specific, and the uncomplicated clinical outcomes of the 18 patients studied, beta-2 transferrin was our standard for comparison with CT (Table 2) and Glucostix (Table 3). CT had a sensitivity of 80%, with 100% positive predictive value for the detection of CSF leaks. Glucostix test strips were non-specific (specificity = 0), and the sensitivity was only 80% when measuring glucose in the nasal and ear discharge of patients suspected of having CSF leaks.

Discussion

About 90% of CSF leaks close spontaneously within 7 to 10 days. The remaining 10% of fistulae persist for more than 1 month. These fistulae carry a high risk for ascending meningitis, the outcome of which may be devastating.[6] Prompt diagnosis and early management of CSF leaks minimize the risks of infection. Intermittent leaks into contaminated body fluids

such as blood, nasal discharge, mucus and tears often make confirmatory diagnoses with traditional methods such as Glucostix difficult.

Table 1. Summary of test results in 18 patients

Patient	Beta-2 transferrin	Glucostix	Computed tomography
1	+	+	–
2	+	+	+
3	+	+	+
4	+	+	+
5	+	+	+
6	–	+	–
7	–	+	–
8	+	+	+
9	–	+	–
10	+	+	–
11	+	+	+
12	+	+	+
13	+	+	+
14	+	+	+
15	+	+	+
16	+	–	+
17	+	–	+
18	+	–	–

Table 2. Comparison of computed tomography (CT) results with beta-2 transferrin assay results

	Beta-2 transferrin		
	Positive	Negative	
CT positive	12	0	PPV = 1
CT negative	3	3	NPV = 0.5
	S = 0.8	SP = 1	

PPV = positive predictive value; NPV = negative predictive value; S = sensitivity; SP = specificity.

Table 3. Comparison of Glucostix results with beta-2 transferrin assay results

	Beta-2 transferrin		
	Positive	Negative	
Glucostix positive	12	3	PPV = 0.8
Glucostix negative	3	0	NPV = 0
	S = 0.8	SP = 0	

PPV = positive predictive value; NPV = negative predictive value; S = sensitivity; SP = specificity.

Detection of glucose in the sample fluid using Glucostix test strips has been the traditional method for detection of the presence of CSF in nasal and ear discharge. Interpretation of the results is confounded by various factors such as contamination from glucose-containing fluid (tears, nasal mucus, blood in nasal mucus) or relatively low CSF glucose levels (meningitis). Most commercial glucose test strips employ the glucose-oxidase enzyme, which causes colour changes to the chromogen, visualized at glucose levels of 4 mmol/L or more. This is at the high-normal reference range for CSF glucose. Glucostix may fail to detect glucose at the CSF low-normal range (2.8–3.5 mmol/L). The value of the Glucostix test should have been discounted after Steedman and Gordon's simple and well-designed study published in 1987.[20] The study discovered that 26% of nasal discharge and tear samples from normal subjects contained glucose levels within the normal range of CSF (2.8–4.2 mmol/L).

Our data suggest that CT may be a useful tool for helping to diagnose and localize clinical CSF leaks. Clinical rhinorrhoea or otorrhoea and a corresponding skull base fracture that has already been located on CT are indicative of a CSF leak; further confirmatory testing is unnecessary. However, CT does miss some fractures, yielding a negative predictive value of 0.5.

Conventional confirmation tests such as cisternography and surgical exploration are invasive.[3–6] Non-specific tests subject patients to unnecessary invasive and risky procedures. Non-sensitive tests delay treatment. The discovery of beta-2 transferrin has solved many of the above problems and can be used to quickly diagnose a CSF fistula.

Beta-2 transferrin is almost exclusively found in CSF. The assay is essentially unaffected by contamination because centrifugation prior to testing removes cellular and large particle contaminants. Furthermore, immunostaining is protein-specific. As little as 2 μL of sample fluid is required for the assay, and extraction of the fluid from an absorptive plug is feasible.

Beta-2 transferrin was reported to have a sensitivity of near 100% and a specificity of about 95% in a large retrospective study.[18] This CSF-specific and protein-specific assay has essentially replaced surgical validation as the test standard.

We do not recommend Glucostix for detection of glucose as a confirmatory test for CSF leaks due to its lack of specificity and sensitivity. In the presence of a radiologically-related (CT) skull base fracture and clinical CSF leak, there is no need for a further confirmatory test. In cases where a confirmatory test is required, beta-2 transferrin assay is the test of choice because of its high sensitivity and specificity. It should be used prior to

invasive procedures for the localization and repair of CSF fistulae.

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