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A modern concept of cerebrospinal fluid diagnosis in oto- and rhinorrhea

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SUMMARY

Three successive CSF investigations make it possible to identify even the smallest amount of cerebrospinal fluid (CSF) in cases of otorrhea and rhinorrhea:

1. *Immunological identification of β_2-transferrin.*
2. *Laboratory fluorescein identification.*
3. *Endoscopic fluorescein detection.*

As a screening procedure the β_2-transferrin identification method is always used as the first step towards clarifying a suspect liquorrhea.

In addition both fluorescein tests are used for the diagnosis depending on the result of the β_2-transferrin identification and further measures. As a result of recent practical experience special attention is paid to the test analyses; the various possibilities of taking samples as well as mailing them. A newly developed diagnostic plan of procedure should (by using practical examples) underline the clinical significance.

This study describes the most up-to-date level in CSF diagnosis and demonstrates that, when combined with a corresponding X-ray investigation, a much more exact range of indication for the surgical treatment of fractures of the base of the skull and CSF leaks is possible.

INTRODUCTION

Cerebrospinal fluid (CSF) egress from the intracranial cavity occurs when the bony protection covering of the skull is opened and the dura and closely adherent outer layer of the arachnoid are incised or otherwise injured. Most frequently it is the result of fractures, but it also occurs after intracranial surgery.

Infections or neoplasia and spontaneous cerebrospinal fluid effusion are less frequently responsible. Many methods which have a more or less restricted diagnostic value have been described in recent years and are still in use. Neither the clinical signs and methods, nor the determination of the glucose and protein content in samples enable an accurate identification of CSF. Hence both methods are, in our opinion, obsolete. All known radioactive methods require a high degree of technology and time investment and the patient must always be

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detained in a special ward. Above all with patients suffering from multiple injuries a rapid CSF diagnosis is restricted, if not impossible. In addition the false positive findings make this method unsuitable in modern medicine. Of all CSF tracing dyes, fluorescein has proved itself to be a very valuable method.
The purpose of this paper is to present two new methods which enable a more accurate CSF identification. In combination with the endoscopic fluorescein test we recommend a modern concept of diagnostic procedure.
The three methods are as follows:

1. Immunological method demonstrating β_2-transferrin (tau band) (Oberascher and Arrer, 1986a, 1986b; 1987).
2. Electrophoretic-photometric method identifying sodium fluorescein (Oberascher and Arrer, 1986).
3. Messerklingers's well proven method of endoscopic fluorescein testing (Messerklinger, 1972).

Consequently we have methods which are more precise than the usual testing procedures of recent decades.

Immunological detection of β_2-transferrin (tau band)
By using the β_2-transferrin method, a protein variant can be identified. This variant is produced by neuraminidase activity of the brain and up to now could only be found in cerebrospinal fluid (CSF). In the analyses of CSF a β_1-transferrin band and a β_2-transferrin band can be demonstrated.
When examining serum, nasal secretion, tears, saliva and/or other body fluids, only one band, the β_1-transferrin band, can be seen. Therefore it is possible to identify CSF accurately. The high sensitivity and specificity of the test depend on immunofixation of the electrophoretically separated transferrin in the agarose gel and on the visualisation of the immune complex by staining with alkaline silver nitrate solution.
Owing to its low content of sialic acid, β_2-transferrin migrates more slowly than the main transferrin component (β_1-transferrin) in electrophoresis (Figures 1 and 2). Since β_2-transferrin occurs practically only in cerebrospinal fluid and not in other body fluids, its detection in secretion from the nose or ear can be used for the diagnosis of rhino- and otoliquorrhea. β_2-transferrin can be identified in 1 µl pure CSF (that corresponds to approx 1/50 of a drop!).
Even under unfavourable conditions (contamination of CSF with nasal or ear secretion) 100 µl CSF can be detected in 1 ml secretion (=2 drops CSF/1 ml). It is possible that disturbing effects may be caused by blood contamination or a high protein content. For this reason haemoglobin must be eliminated by using chromatography. Furthermore, it is necessary to reduce a protein content of more than 5 g/l with ammonsulfat precipitation. If care is taken in respect of these two points, disturbing effects can be avoided. This method satisfies five require-

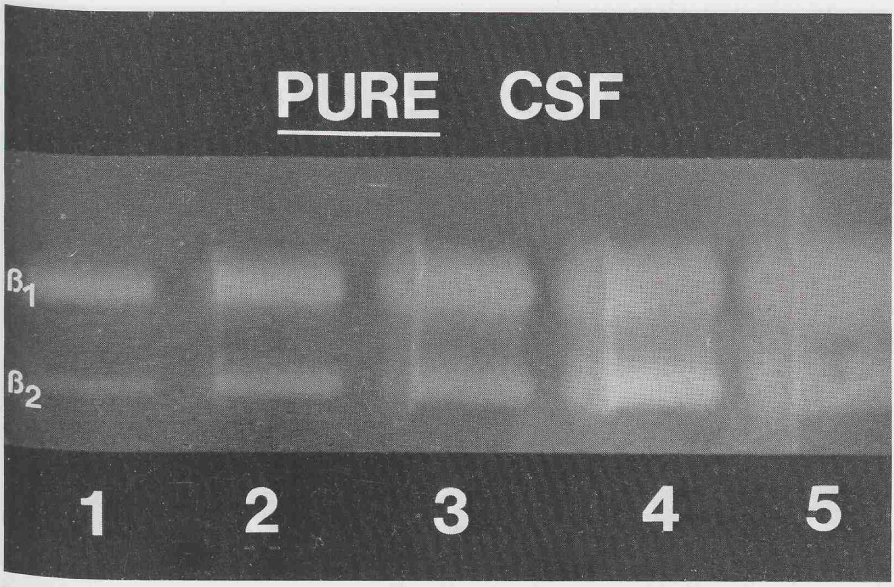

Figure 1. **β_2-transferrin (tau band) identification:** Agarose-gel electrophoresis of pure cerebrospinal fluid (CSF) after immunofixation and silver staining.
position 1: 10 µl CSF
position 2: 20 µl CSF
position 3: 40 µl CSF
position 4: 80 µl CSF
position 5: 200 µl CSF
β_1 = β_1-transferrin band
β_2 = β_2-transferrin band (typical of CSF)

ments, which are important in the modern investigation of cerebrospinal fluid:

1. high rate of accuracy
2. wide area of application
3. rapid availability
4. high sensitivity
5. no risks to the patient.

Quality control

For exact quality control of this method a 5 µl sample of pure CSF should always be analysed at the same time. This analysis will always indicate a β_2-transferrin band which is readily available for comparison should the sample analyses prove positive. At the same time it is imperative to examine the patients serum. In this way false indications of positive findings, such as in patients with liver cirrhosis or those with genetic protein variants are eradicated.

In the case of five patients with liver cirrhosis, we detected two additional bands,

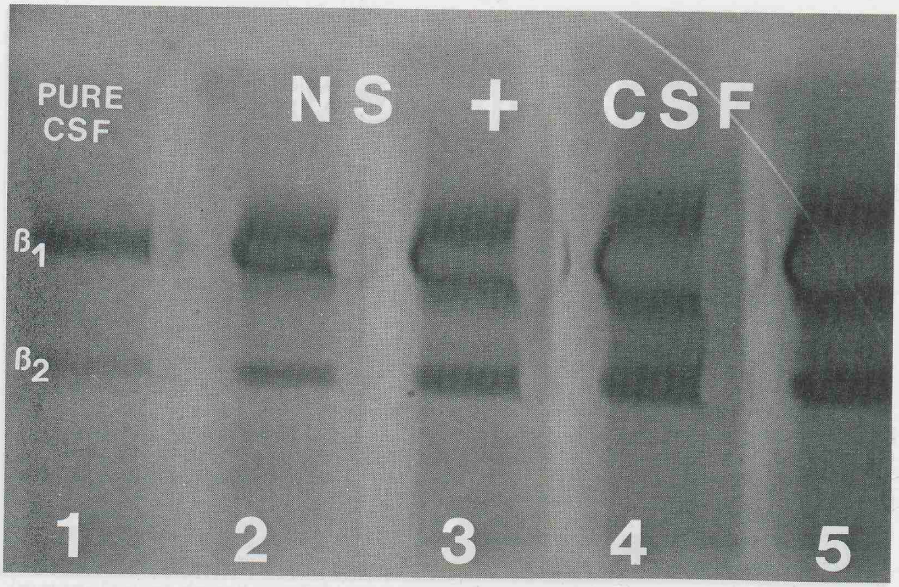

Figure 2. β_2-transferrin identification:
Cerebrospinal fluid mixed with nasal secretion
position 1: 2 µl pure CSF
position 2: 1 ml ns and 200 µl CSF
position 3: 1 ml ns and 400 µl CSF
position 4: 1 ml ns and 600 µl CSF
position 5: 1 ml ns and 800 µl CSF

which were located at the same height as the tau band. In all five cases there was no question of CSF leakage. The sample analysis which was of greatest clinical relevance was that of a young man whose nasal secretion and also serum indicated a β_2-transferrin band. The fact that this was actually a case of genetic protein variants was proved by a repetition of this pattern in some members of the patients close family.

Mailing of samples

When posting samples the following points should be taken into consideration. For each patient 2 ml of serum must be sent in addition to the samples of nasal or ear secretion. Cooling of samples is not necessary. The size of the test tubes used for the samples should be as small as possible.

Rhinorrhea without previous trauma

In the cases of patients with continual or only occasional secretion from one or both nostrils we must differentiate between the so-called spontaneous CSF rhinorrhea or the one caused by intracranial tumours and rhinorrhea caused by

non allergic vasomotor rhinitis, infectious – allergic rhinosinusitis, allergic rhinitis or cyst fluid from the maxillary sinus.

Where there is sufficient secretion, samples can be collected in a test tube. If there is too little fluid or if the question of localisation arises we insert sterile Merocel® nose sponges into the right and the left nose as far as the nasopharynx (Figure 3). They are left in place for six hours to provide an adequate sample. Besides the determination of β_2-transferrin we perform skin tests, in vitro tests such as PRIST and RAST on the serum and nasal secretion as well as the rhinomanometric controlled nasal provocation test.

CSF rhinorrhea after trauma

Any accidental breach of the bony protective covering of the brain and its contents coupled with a rent in the protective membranes covering the brain results in a communication of the subarachnoid space with the outside environment and from this point a release or leak of cerebrospinal fluid is caused (Lewin, 1954; Vrabec, 1964; Grahne, 1970; Chidlow, 1973; Hudson, 1975; McCabe, 1976). Undoubtedly this occurs very frequently as a consequence of severe head trauma in which the cranial vault or base of the skull is fractured. This is usually caused by blunt trauma. Fractures through the anterior cranial fossa, like those through the posterior wall of the frontal sinus, roof of the orbit, or roof of the ethmoidal sinuses and cribiform plate, communicate directly with the intranasal space (Ray and Berglund, 1969; Brisman et al., 1970). Then the leakage of cerebrospinal fluid takes place from the nose. It is not even noticed in many instances because of other serious injuries usually accompanying such fractures. Airway problems, bleeding, other obvious compound fractures, and abdominal and thoracic injuries usually demand the immediate attention of the trauma, and little or no attention is paid to any drainage from the nose, or back of the throat.

Therefore a patient who has been injured recently and whose X-ray shows head fractures and who has nasal secretion, immediately receives sterile Merocel® nose sponges, which are placed into both nasal cavities and left there until they have soaked up sufficient secretion. This procedure has the advantage that a CSF leakage, which sometimes stops after a few days or is clinically not visible, can be identified at the very moment. Furthermore it enables us to make an accurate diagnosis of either side.

Generally the traumatic cerebrospinal fluid leak is iatrogenic and can occur after standard neurosurgical procedures, as well as a variety of nose and sinus operations (Chandler, 1970). During intranasal operations such as ethmoidectomy, septorhinoplasty, polypectomy and even simple submucous resection of the nasal septum, undue or inadvertent force may result in a fracture through the cribiform plate area, or more likely through the roof of the ethmoidal labyrinth resulting in a leakage of cerebrospinal fluid. Surgical procedure performed upon

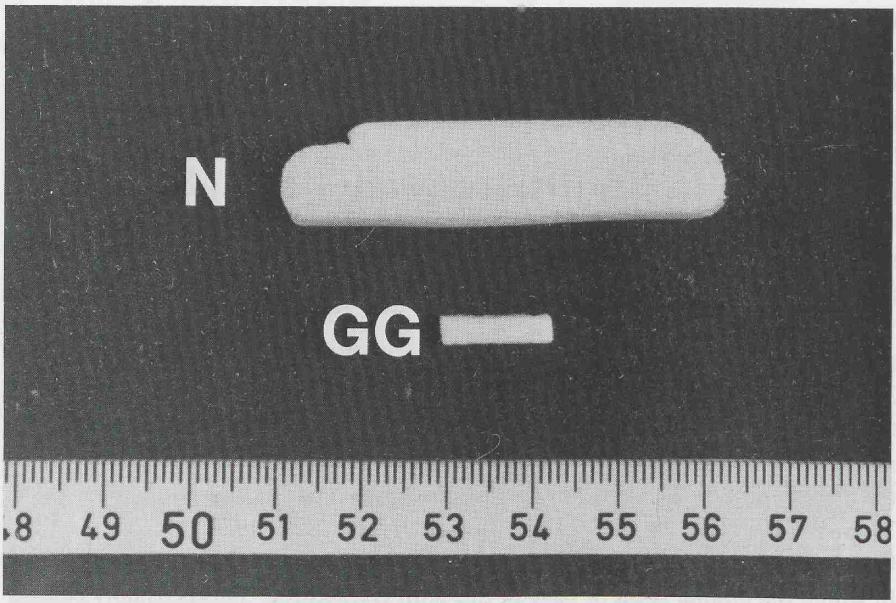

Figure 3a. β_2-transferrin analyses: Dry Merocel ear (GG) and nose (N) sponges previous to insertion.

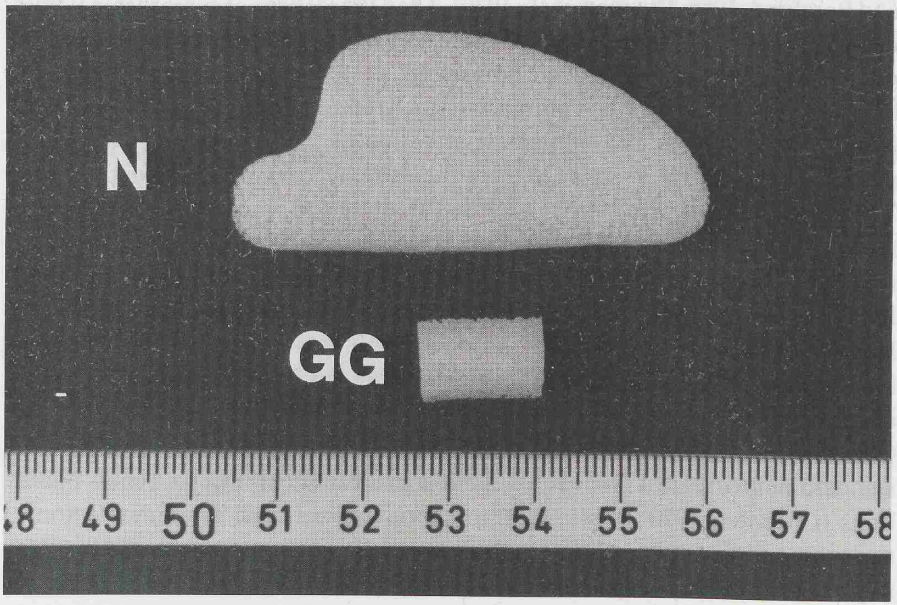

Figure 3b. β_2-transferrin analyses: Merocel ear and nose sponges soaked up with sufficient secretion for testing.

the frontal, ethmoidal or sphenoidal sinus can result in disruption of the bony floor of the anterior cranial fossa and disruption or interruption of the soft tissues at the base of the brain. In all cases with enough discharge of fluid we collect a sample in a test tube. If not Merocel® nose sponges are inserted and not removed before six hours (Figure 3).

CSF otorrhea

CSF egress from the subarachnoid space into the pneumatized spaces of the temporal bone is usually the result of a fracture together with a laceration of the dura and arachnoid. They are usually of the longitudinal type, which disrupts the tympanic membrane along with the floor of the middle or posterior cranial fossa (Hicks, 1980). Intracranial surgery that extends through or into the temporal bone is the next most common cause.

Infection or neoplasia are less frequently responsible. These forms of CSF fistulae are more common [in approximately 90% of the cases (Ray and Berglund, 1969)] than the spontaneous types which are caused by congenital malformations - e.g. deformed petrous bone in the so-called Mondini-type (Litière and Koch, 1984).

Leakage of CSF from the pneumatized spaces to the external environment is frequently caused by fractures, erosions, or lacerations in the tympanic membrane and external auditory canal or by surgical wounds. When these external passages are intact, the fluid may leak through the Eustachian tube, thus becoming CSF rhinorrhea. If the flow is not sufficient for the fluid to discharge from the anterior nares it may easily go undetected until recurrent meningitis suggests its presence.

The way of taking samples depends on the situation (Oberascher, 1987).

1. If there is sufficient and clear fluid, it can be collected in a test tube.
2. In the case of temporal bone fractures with perforation of the ear drum we always insert Merocel® ear sponges into the external auditory meatus and leave them in place for twelve hours (Figure 3).
3. Should there be CSF in the middle ear cavity behind a closed ear drum we puncture it.
4. If CSF passes through the tuba auditiva into the pharynx, it can be collected by inserting a Merocel® tube sponge into the pharyngeal orifice of the tube (Figure 4).

Case material (β_2-transferrin analysis)

The β_2-transferrin investigation has so far been carried out in 88 patients (Table 1). In 34 cases a β_2-transferrin band, i.e. CSF, could be demonstrated. However, in only one case, that of a young man, the result was false positive as a β_2-transferrin band could be seen in nasal secretion as well as in blood serum. In this

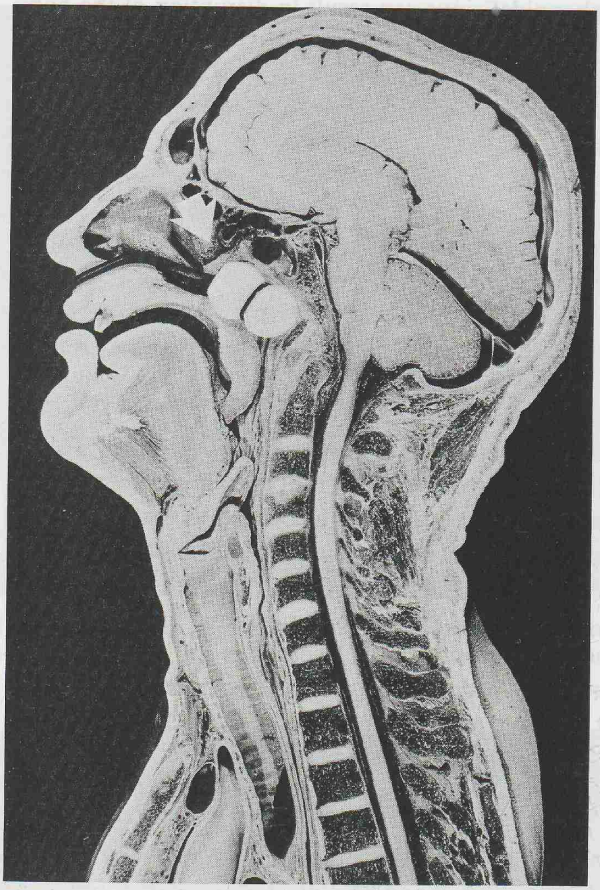

Figure 4. β_2-transferrin analyses: Merocel® tube sponge – placed on the pharyngotympanic ostium.

Table 1. β_2-transferrin investigations. Number and cases of analysed samples.

	n	pos.	false pos.	neg.	false neg.
CSF rhinorrhea					
base of skull fractures	23	10	1	10	2
after rhino-surgery	4	4	–	–	–
CSF otorrhea					
temp. bone fractures	21	11	–	10	–
non allergic vasomotor rhinitis	23	–	–	23	–
wound secretion					
(after neurosurgical procedure)	2	2	–	–	–
mailed samples	15	6	–	9	–
total	88	33	1	52	2

situation the immunological test is of no use. We therefore examined all the members of the patient's family and found that the mother and four out of the six brothers and sisters also had positive test results. But in these cases the band had to be interpreted as a genetic protein variant. This example emphasises that an analysis of a patient's blood serum is always necessary. This meant that there were 33 positive β_2-transferrin results. Fourteen of these patients suffered from CSF rhinorrhea with an intraoperative confirmed CSF fistula in the lamina cribosa and the sphenoid. In only five cases was CSF clinically visible. Ten patients had a recent fracture of the frontal base of the skull, four had injuries of the dura at the rhinobase which had occured some years before. The remaining six positive tests were from secretions sent by other hospitals. Therefore we do not know the full history of these patients yet. Of the 19 negative results of this group nine samples were sent to us from other clinics and ten came from our own case material. After taking X-rays of the fractures of the rhinobase with bone dislocation eight of these patients were operated on. In six cases there were no dura injuries, but two patients had a small (approximately 3 mm long) dura fistula in the middle of the lamina cribrosa. A clinical rhinoliquorrhea after the injury was not found in any of the cases.

The two false negative results can best be explained by a lack of liquorrhea when the samples were being taken. An edema of the bordering brain tissue or a bone splinter could be possible causes of the sealing up of dura fistula. Furthermore, all fluorescein tests were negative in both cases. Of 21 patients with suspected otoliquorrhea, perforated ear drum and temporal bone fractures as shown by X-rays, 11 had a positive result and 10 a negative.

In seven patients with a positive β_2-transferrin test a spontaneous healing of the ear drum occured, and therefore surgery was not necessary. In the remaining four cases a dura fistula was detected intraoperatively. In two other patients who had just had neurosurgery on the posterior and middle cranial fossa, CSF could be identified in the discharged wound secretion. During the next operation a dura lesion was actually found.

Electrophoretic-photometric identification of 5% sodium fluorescein

In order to be able to trace CSF the usage of colour dyes, such as 5% sodium fluorescein, for the identification of oto- and rhinoliquorrhea, proved to be especially efficient and is therefore still used in many clinics. This method was introduced by Kirchner and Proud (1960) and was later refined by Messerklinger (1972). The test involves intrathecal injections of fluorescein with 2 cc injected into lumbar sites.

We have developed a more refined and new method for the identification of sodium fluorescein in cases of CSF leakage. (Oberascher and Arrer, 1986). In order to take samples, three small Merocel® sponges are always placed into each

nasal cavity immediately after injection of 2 cc 5% sodium fluorescein (Figure 5). They are left in place over night and are removed the next morning before nasal endoscopy is performed. Fluorescein is identified by electrophoretic separation on 1% agarose gel and by a demonstration with the fluorescein photometer (Figure 6). This method of testing has various advantages:

1. Isolation of the specific site of the leak.
2. Topodiagnostic investigation (frontal region, ethmoid or sphenoid region).
3. The use of sponges enables the collection of maximal amounts of CSF. A leakage can be clearly identified even in quantities of 2 µl per 1 ml secretion.
4. Potential sources of disturbance (e.g. haemoglobin, etc.) are eliminated.
5. False-positive results are avoided, because of the high speed at which fluorescein moves.
6. The time needed for sample analyses is only ten minutes.

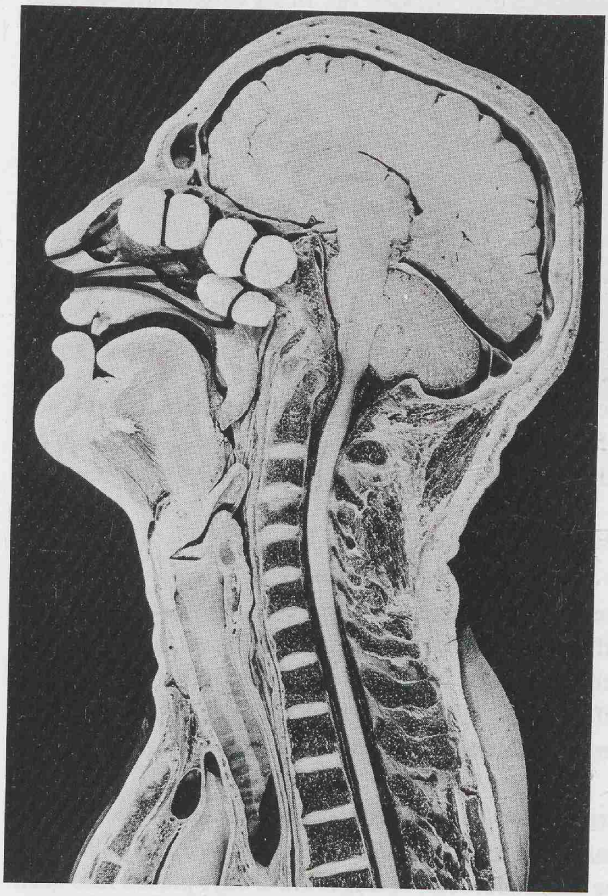

Figure 5. Laboratory fluorescein identification of sodium fluorescein: For sample collection three Merocel® sponges are placed into each nasal cavity.
Advantages of this procedure:
1. Isolation of the specific site of leak
2. Topographical identification (frontal-ethmoid or ethmoid-sphenoid region, pharyngo-tympanal ostium)

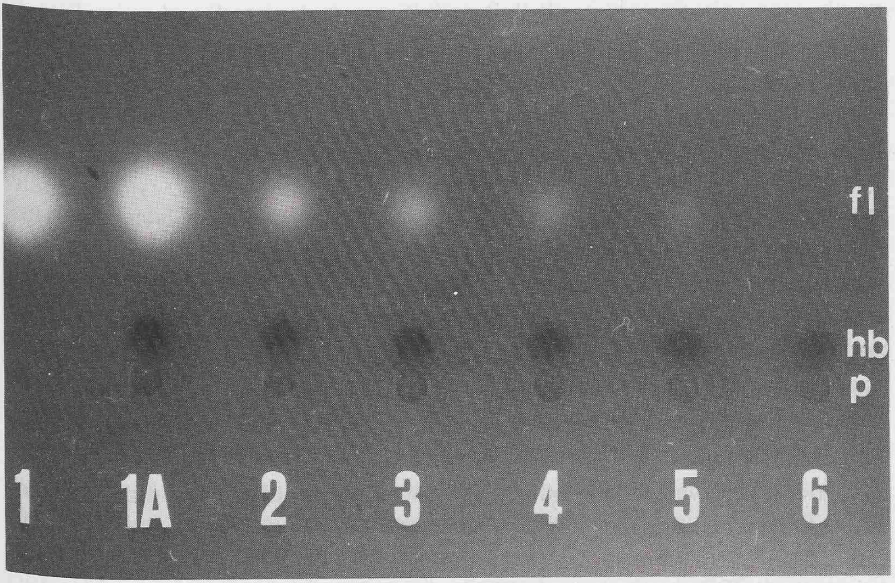

Figure 6. Agarose-gel electrophoresis of sodium fluorescein, CSF and haemoglobin solution; sample volume 15 µl.
Sample 1: CSF with fluorescein; dilution 1:200.
Sample 1A–5: CSF with fluorescein and haemoglobin.
Dilution 1:200 (A), 1:10000 (2), 1:20000 (3), 1:100000 (4), 1:200000 (5).
Sample 6: pure CSF.
p = punched hole in gel.
hb = haemoglobin.
fl = fluorescein.
haemoglobin concentration: 3g/dl.

By using our test method in clinical studies, we tried to identify even the smallest quantities of fluorescein-stained CSF in rhinoliquorrhea and to eliminate all possible sources of error in testing as described by Simon (1970). Our test analyses with electrophoresis showed that fluorescein was the fastest moving substance on agarose gel and could be found as the substance the furthest away from its initial wall on the gel. All other substances e.g. haemoglobin, serumprotein, even those with their own fluorescent qualities e.g. Tetracyclin, were found to stop moving sooner (Figure 6). Thus, the fluorescein could always be completely identified. Because of its high sensitivity this method has the advantage that it makes the identification possible of amounts of CSF which could possibly go unnoticed using the endoscopic or immunochemical method.

Endoscopic identification of 5% sodium fluorescein (according to Messerklinger)
Using Messerklinger's endoscopy, both nasal cavities can be explored precisely and so it is possible to describe an existing CSF leakage topographically.

Equipment:

1. Hopkins optics
2. cold light source
3. blue light filter
4. complementary barrier filter (placed in front of the ocular of the Hopkins optic).

The fluorescein tests are carried out on the following patients:

1. Preoperatively, in cases where surgery of base of skull fractures and/or closure of a persistent CSF leak is planned. The advantage is that during surgery minimal dura lesions can be detected better because of traced CSF.
2. On patients with possible dura fistula after earlier head injuries or rhinosurgery with delayed rhinorrhea.
3. In all cases with a false-positive immunological test (liver cirrhosis, genetic protein variants).

All patients receive 2 ml 5% sodium fluorescein intrathecal into lumbal sites one day before nasal endoscopy and/or surgery.

The benefit of this procedure is that:

1. In cases where surgery is necessary, the patient is not subjected to anaesthesia and fluorescein testing on the same day.
2. For the laboratory chemical fluorescein test Merocel® nose sponges can be inserted into both nasal cavities and left in place overnight.

We do not administer sodium fluorescein to patients with meningitis, epilepsy, circulatory shock, or to those who do not have a strong constitution in general and also not immediately after trauma, and during general anaesthesia. In recent years we have carried out fluorescein tests on more than 200 patients. Taking all the points mentioned above into consideration we did not come across any harmful side-effects or complications, although the occurrence of side-effects is described in the literature (Mahaley and Odom, 1966; Moseley, 1968; Wallace, 1972; Mees and Beyer, 1982).

Case material (fluorescein test)

As the laboratory test has only been developed recently, we have carried out the laboratory fluorescein identification as well as endoscopic fluorescein diagnosis according to the diagnostic procedure on not more than 13 patients. In ten cases both investigations were negative including the β_2-transferrin results. Two patients with intraoperative confirmed dura lesion showed a positive result in both fluorescein and the β_2-transferrin tests. One of the two patients had a frontobasal fracture with bone dislocation on one side, identified in X-rays. Of the three tests only the laboratory fluorescein test was positive. As the patient refused surgery the dura fistula which was certainly present could not be confirmed.

This last case confirms our experimental analyses (Oberascher and Arrer, 1986) which predicts that in the case of subclinical liquorrhea the laboratory fluorescein

identification has the greatest sensitivity of all three investigation procedures. With a positive laboratory fluorescein result a dura lesion can always be considered present as false-positive results can be excluded because of the test situation and specification.

DISCUSSION

Immunological CSF identification by means of β_2-transferrin and laboratory fluorescein identification both, developed by us, have given new impulses to the diagnosis of CSF of oto- and rhinorrhea. In combination with the endoscopic fluorescein diagnosis, a modern diagnostic plan has been developed which makes CSF and dura fistula identification more accurate than ever before. All other methods which have been developed and described so far (chemical: glucose- and protein level or CSF-tracing e.g. radioactive isotops, X-ray contrast medium) diagnosing liquorrhea are obviously inferior and should no longer be employed. β_2-transferrin investigation, as a screening method, should always be carried out first. As a non-invasive method it does not put the patient at any risk, and it can be repeated as often as required and it also guarantees, even in the case of subclinical CSF leakage the accurate identification of CSF. In 1 µl of pure CSF the β_2-transferrin band is clearly identifiable. If the amount of contaminated nasal or wound secretion is too high (usually with samples from sponges) CSF identification is sometimes no longer possible (identification limit 100 µl/ml secretion). In this case, principally preoperatively and in patients with previous meningitis and head injuries we employ both fluorescein investigations. The laboratory fluorescein identification has the highest sensitivity level of all three methods because in this method even 2 µl traced CSF per ml secretion in the analyses of samples taken from sponges can be detected. Furthermore, apart from identifying even the smallest amounts of CSF as a result of separate analyses of all six Merocel® sponges, a specific topodiagnostic exploration is possible. The endoscopic fluorescein diagnosis is always carried out at the end of our diagnostic procedure because of technical reasons. As an optical instrument for the direct and immediate inspection of the nasal cavity and of CSF fistula along the rhinobase it is a very useful and indispensable examination.

It can be concluded that our diagnostic plan using the three different methods of investigation is the most accurate and up-to-date procedure for diagnosing CSF otorrhea and rhinorrhea. In combination with X-ray diagnosis, especially computed tomography, a much more precise indication for surgical treatment of fractures of the base of the skull is possible.

ZUSAMMENFASSUNG

Folgende drei liquordiagnostische Untersuchungen ermöglichen die Erfassung und den Nachweis noch kleinster Liquormengen bei einer Oto- oder Rhinoliquorrhoe:

1. Immunologischer Nachweis mittels β_2-Transferrin.
2. Laborchemische Fluorescein-Identifikation.
3. Endoskopische Fluorescein-Diagnostik.

Als Screeningverfahren und Methode der Wahl steht die β_2-Transferrinbestimmung grundsätzlich am Beginn der Abklärung einer suspekten Liquorrhoe. Je nach Befund bzw. in Abhängigkeit weiterer Maßnahmen werden die beiden Fluorescein-Nachweisverfahren zusätzlich zur Abklärung herangezogen. Aufgrund in letzter Zeit gewonnener praktischer Erfahrungen wird insbesondere auf die Probenanalyse, die verschiedenen Möglichkeiten der Probengewinnung und den Probentransport eingegangen.

Ein neu entwickelter diagnostischer Stufenplan soll anhand von praktischen Beispielen den hohen klinischen Stellenwert aufzeigen. Dieses Konzept stellt den zur Zeit modernsten Stand der Liquordiagnostik dar und zeigt auf, daß in Kombination mit einer entsprechenden röntgenologischen Diagnostik eine wesentlich exaktere Indikationsstellung zur Revision von Frakturen der Rhino- und Otobasis ermöglicht wird.

REFERENCES

1. Brisman R, Hughes J, Mount L. Cerebrospinal fluid rhinorrhea. Arch Neurol 1970; 22:245–252.
2. Chandler JR. Iatrogenic cerebrospinal rhinorrhea. Trans Am Acad Ophthalmol Otolaryngol 1970; 74:576–584.
3. Chidlow JH. The diagnosis, localisation and treatment of CSF rhinorrhea. ORL Digest 1973; 9–13.
4. Grahne B. Traumatic cranionasal fistulas, persistent cerebrospinal fluid rhinorrhea and their repair with frontal sinus osteoplasty. Acta Otolaryngol 1970; 70:392–400.
5. Hicks GW. Cerebrospinal fluid otorrhea. Laryngoscope 1980; (Suppl 25):90.
6. Hudson WR, Hudhes LA. Cerebrospinal rhinorrhea. South Med J 1975; 68:1520–1523.
7. Kirchner FR, Proud GO. Method for the identification and localisation of cerebrospinal fluid. Rhinorrhea and otorrhea. Laryngoscope 1960; 70:921–931.
8. Lewin W. Cerebrospinal fluid rhinorrhea in closed head injuries. Br J Surg 1954; 42:1–18.
9. Litiére L, Koch U. Felsenbeindysplasie Typ Mondini als Ursache einer spontanen Otoliquorrhoe. Laryng Rhinol Otol 1984; 63:389–391.
10. Mahaley MS, Odom GL. Complication following intrathecal injection of fluorescein. J Neurosurg 1966; 25:298–301.
11. McCabe BF. The osseo-mucoperosteal flap in repair of cerebrospinal fluid rhinorrhea. Laryngoscope 1976; 86:537–539.
12. Mees K, Beyer A. Akute neurologische Komplikationen nach intrathekaler Fluoresceininjection. Laryng Rhinol Otol 1982; 61:102–104.
13. Messerklinger W. Nasenendoskopie: Nachweis Lokalisation und Differentialdiagnose der nasalen Liquorrhoe. HNO 1972; 20:268–271.
14. Moseley JI. Spectrum of complications in the use of intrathecal fluorescein. J. Neurosurg et al 1968; 48:765–769.

15. Oberascher G, Arrer E. Immunologische Liquordiagnostik mittels β_2-Transferrin - Grundlagen und Methodik. Laryng Rhinol Otol 1986a; 65:158–161.
16. Oberascher G, Arrer E. Erste klinische Erfahrungen mit β_2-Transferrin bei Oto- und Rhinoliquorrhoe. HNO 1986b; 34:151–155.
17. Oberascher G, Arrer E. Efficiency of various methods of identifying cerebrospinal fluid in oto- and rhinorrhea. ORL 1987; 48: 320–325.
18. Oberascher G, Cerebrospinal fluid otorrhea - new trends in diagnosis. Am J Otology 1988; (in press).
19. Oberascher G, Arrer E. A new method for using fluorescein to demonstrate oto- and rhinoliquorrhea I. Sample preparation by electrophoresis and photometric identification of fluorescein. Arch Otorhinolaryngol 1986; 343:117–120.
20. Ray B, Berglund P. Cerebrospinal fluid fistula: Clinical aspects, techniques of localisation and methods of closure. J Neurosurg 1969; 30:300–405.
21. Simon H. Die Fluoresceinprobe zur Diagnostik der oto- und rhinogenen Liquorfistel. Laryngol Rhinol 1970; 49:54–60.
22. Vrabec DP, Hallberg OE. Cerebrospinal fluid rhinorrhea. Arch Otolaryngol 1964; 80:218–229.
23. Wallace JD. Status epilepticus as a complication of intrathecal fluorescein. J Neurosurg et al 1972; 36:659–662.

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