CEREBRAL ANGIOGRAPHY: TOLERANCE FOR CONTRAST MEDIA OF DIODRAST TYPE

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Cerebral angiography was introduced by Moniz in 1927. Although increased experience has widened the indications for the method, its general application has been limited because of the difficulty of the injection technique and because of some undesirable results obtained with the use of the contrast media hitherto available.

The operative exposure of the carotid artery limited the application of the method, but this objection has been overcome by the percutaneous technique adopted by Loman and Myerson (1936), which paved the way for a wider use of the procedure (Engeset, 1944; Lindgren, 1947; etc.).

As all the contrast media available for cerebral angiography are capable of causing complications, it is difficult to determine which should be given preference. The undesirable results obtained with sodium iodide, the first medium used in this method, were avoided later by the use of thorotrast, which was then used extensively. This medium, however, has an irritating effect on the tissues, and in the course of time large injections are liable to give rise to sarcomas, not only in experimental animals, but also in man (MacMahon and others, 1947). Even a small dose involves certain risks, for extravascular deposits of the substance are capable of causing large cicatricial formations and granulomas in the neck (Ziffren, 1940; Sjökvist, 1948) of the type that have been known to develop after the use of thorotrast in retrograde pyelography.

It was mainly for these reasons that the use of radiopaque substances of the Diodrast type was adopted for cerebral angiography (Gross, 1939). These substances have proved on the whole satisfactory. They have, however, one inherent disadvantage: they irritate the vessel wall unduly, and this may sometimes cause complications. In two of three cases in which Dyke (1940) used a 70 per cent. solution of Diodrast the results were dramatic, for in one case there developed thrombosis of the common carotid artery, and in the other prolonged loss of consciousness. Collins (1947)

was reported to have had a fatal case. The occasional occurrence of epileptic fits, though generally slight, have been reported by Gross (1939), Engeset (1944), Lindgren (1947), and Wickbom (1948).

As thorotrast causes no immediate complications and has good radiopacity, its use is still sometimes recommended in spite of the obvious risks involved (List and others, 1945; Govons and Grant, 1946; Hodes and others, 1947; Hodges, 1947). As, however, the water-soluble contrast media are clearly preferable, the writer decided to investigate the tolerance for contrast media of the Diodrast type, as this question has apparently not been adequately studied.

Since the institution of the Neuro-Roentgenological Laboratory of Lund in 1946, contrast media of the Diodrast type have been used and the tolerance of the patients for these substances closely observed. Our experience is reported here. It should, however, be observed that only the tolerance for the contrast media will be discussed, our material still being insufficient to elucidate the diagnostic value of the method. Those desiring information on the latter subject are referred to Wickbom's (1948) "Angiography of the Carotid Artery."

Material

The material comprises all cerebral angiographic examinations made in 1947 and 1948 by the same technique at the Neuro-Roentgenological Laboratory, Lund, and consists of 277 patients, or 336 cerebral angiographic series. In 31 cases angiograms were made bilaterally. The age of the oldest patient examined was 74 years, and of the youngest 3 years. Ninety-six of the patients were over 50 years old, and 8 were under 15 years. Emergency examinations were made in 21 cases, in most of which the patients were unconscious. The material consisted of 183 patients from the Neurosurgical Department, 73 from the Medical and Neurological Departments, and 21 from other departments.

The conditions which were investigated were: cerebral tumour, 101 (17 of which were not verified, mainly central gliomas); sequelæ of head injuries, 23; vascular lesions, 29; arterial or arterovenous aneurysm, 12; cryptogenetic epilepsy, 29; other neurological states, 71.

Technique

The technique adopted followed that suggested by Lindgren (1947). Usually we take stereoscopic lateral angiograms (each of which requires a separate injection) and also frontal pictures, which means that three injections are necessary for each examination.

As the branches of the internal and external carotid arteries are easily distinguished in stereoscopic angiograms, and filling of the branches of the external carotid artery is often desirable, the injection is usually made by puncture of the common carotid artery. The carotid artery was punctured percutaneously in 323 of 330 angiographic examinations, and in 7 cases the carotid artery was exposed. In 3 cases the patients were examined under narcosis.

The contrast media used were almost exclusively Umbradil (35 per cent.), the diethyl salt of 3·5 diiodopyridone-N-acetic acid, and Umbradil Forte (50 per cent.), a combination of the diethyl salt and the dietanolaamine salt of the same acid (supplied by AB Astra, Sweden).

Reactions

Reactions were observed in 21 of the 330 examinations. These do not include those cases of transient pain, brief malaise after the injection, slight allergic symptoms such as a local reddening of the skin, or a few isolated urticarial eruptions.

In 16 cases the patients were slightly febrile (37·6 to 37·8° C.; 99·7 to 100° F.) on the day after examination. The temperature returned to normal after two or three days. A strong allergic reaction was observed in 2 cases. In one of them a marked though brief facial swelling was observed after an injection of 8 ml. radiopaque substance. The reaction in the other case was of a far more serious nature.

A man, 27 years old, had a head injury and lost consciousness. After the accident he suffered from headache, vomiting, and dizziness. Cerebral angiography was carried out on the left side. An injection of 10 ml. Umbradil (35 per cent.) was made into the common carotid artery without any reaction. Three minutes later a second injection was made. Seven minutes after this the patient turned pale and the skin became cold and clammy. The eyelids were markedly swollen. The patient could not speak, and began to gasp for breath. Artificial respiration was carried out and an intravenous injection of calcium was given immediately. After a few minutes respiration was normal, and after ten minutes the patient was able to speak without trouble. The facial swelling subsided

quickly, and after forty-five minutes there was only slight oedema of the eyelids and the lips.

In three other cases cerebral angiography was followed by considerable deterioration in the general condition of the patient.

Case 1.—A man of 42 years, who had been languid for four months, on Jan. 13 complained of severe right unilateral headache and numbness of the entire left half of the body. On Jan. 19 the headache, numbness, and langour recurred. Since then the headache had persisted and the patient had become increasingly apathetic. Radiographs of the skull were normal.

Cerebral Angiography.—The common carotid artery was punctured percutaneously, and two injections of 10 ml. Umbradil Forte (50 per cent.) were given with an interval of about three minutes. The films showed that almost all the injected substance had swept through the trunk and branches of the external carotid artery. There was also retrograde filling of the common carotid down to the innominate artery, from where the contrast medium had flowed up into the vertebral artery. The trunk of the internal carotid artery was filled completely with contrast medium for about 1 cm. from the bifurcation. Here a filling defect in the vessel was discerned. A small quantity of the radiopaque substance had passed along the dorsal border of the vessel up to the carotid syphon. In the angiograms made with the second injection the filling defect 1 cm. from the bifurcation of the internal carotid artery was more distinct. The defect was of irregular outline and about 1 cm. long. Beyond it the contrast medium again filled the greater part of the internal carotid artery up to the syphon. Four seconds later the radiopaque substance had passed on through the internal carotid artery and filled the branches of the anterior cerebral artery and the middle cerebral artery. Thus, four seconds after injection the substance had not passed over into the veins but was still manifest in the arteries.

Radiological Diagnosis.—On the radiological evidence a diagnosis was made of thrombosis of the internal carotid artery with considerable slowing of the blood stream in this artery and its branches.

In the evening of the same day a left facial paresis, considerable loss of gross functional power of the left arm, and a left positive Babinski's sign were recorded. The following day the symptoms were more pronounced. No further changes were observed in the patient's condition for about a month, after which he began to recover gradually.

The day after the angiographic examination a temperature of 38·1° C. (100·6° F.) was registered, which afterwards dropped gradually. The temperature did not return to normal until five days after the examination.

Case 2.—A woman of 55 years had acute paresis of the left oculomotorius in April 1948. No other neurologic symptoms were observed. Lumbar puncture showed nothing pathological. The Wassermann reactions in blood and cerebrospinal fluid gave negative results. Plain radiographs of the skull were normal.

Cerebral Angiography.—The left common carotid artery was punctured percutaneously and 10 ml. of Umbradil (35 per cent.) was injected. Three minutes later a second injection of 10 ml. Umbradil Forte (50 per cent.) was made. The contrast filling of the external carotid artery and the internal carotid artery and its branches was good. The branches of the internal carotid were tortuous and of reduced lumen, indicating arteriosclerosis. The rate of flow of the contrast substance did not seem irregular.

About two hours after the examination the patient was mentally confused. She could not follow a conversation. The following day the patient's mind was clear and her general condition was again the same as the day before the examination. The patient's temperature, which had been normal before, rose to 38.4° C. (101.1° F.) on the evening of the examination day. The temperature fell gradually and was normal again on the fourth day.

Case 3.—A woman aged 51 years, since 1944 had suffered from attacks of headache, vomiting, dizziness, and double vision. Since January 1944 there had been a left hemiparesis, and since March 1947 a right facial paræsthesia. During the last six months the patient had become apathetic and her memory was failing. Examination showed disturbance of facial sensation on right side, left facial paresis, paresis of the left arm and leg, homolateral positive Babinski's sign, and bilateral papilloedema of about 3 D. Plain radiographs of the skull were normal.

Cerebral Angiography.—Percutaneous puncture of the right common carotid artery was performed. Two 10 ml. injections of Umbradil Forte (50 per cent.) were given with a three-minute interval. A considerable upward displacement of the vessels of the sylvian group was observed, indicating a temporal tumour. The flow of the radiopaque substance through the internal carotid artery was abnormally slow; even four seconds after injection the substance was still in the capillary phase and not yet discernible in the veins.

After examination the patient became more drowsy and apathetic, while the paresis was accentuated. On the day after the injection the temperature was 38.1° C. (100.6° F.). It fell on the third day, but the patient was still subfebrile six days later, when operation revealed a large cystic astrocytoma in the temporal lobe.

Discussion

The reactions observed after cerebral angiography may be divided into three groups.

Group I.—The characteristic feature of this group is slight fever. This was the only symptom in 16 cases. The temperature rose to between 37.6 and 37.8° C. (99.7 to 100° F.) on the day of the examination or the day after, to return to normal on the second or third day. The most reasonable explanation of this reaction is the formation and absorption of a hæmatoma subsequent to arteriopuncture and in a few, especially in hypertensive cases, palpable

hæmatomata were observed. No shortness of breath or other symptoms supervened in these cases. This explanation is supported by the fact that fever developed in one case in which no radiopaque injection was made because a hæmatoma developed in association with the puncture.

It should be observed that the serious reactions seen in Group III were also accompanied by raised temperatures, that were, however, both higher and more persistent than in this group.

Group II.—This group is characterized by a hypersensitivity of the patient to the contrast medium used. Reactions due to such specific allergy are common and result in slight malaise after the injection of contrast media for different purposes (urography, phlebography, arteriography). Small urticarial eruptions are also relatively common. Such marked allergic reactions as in Cases 1 and 2, are, however, uncommon. Nevertheless we know that the allergic reaction is, though rarely, capable of ending fatally, the latest report of such an accident probably being that published by Simon (1948). The best way of avoiding such accidents is to inquire carefully into any history of allergic reactions and to examine for hypersensitivity by means of a small test-injection of the proposed contrast medium. At the Neuro-Roentgenological Laboratory, Lund, the patient is generally given a test injection of 1 to 2 ml. intravenously at least half an hour before the examination proper, and observed for allergic symptoms.

It should, however, be emphasized that allergic reactions cannot be avoided altogether, and that in laboratories where injections of any of these contrast media are made an emergency tray with suitable injection solutions, an intubator, and apparatus for artificial respiration should always be near at hand.

Group III.—This group of reactions, which constitute a type not mentioned previously in the literature, is of great interest. In two of these cases a vascular lesion was diagnosed clinically. On x-ray examination a thrombosis of the internal carotid artery was diagnosed in one case, and arteriosclerotic vascular changes in the other. In the third case a large temporal astrocytoma was found at operation. In all three cases the general condition of the patients deteriorated considerably after the angiogram.

The deterioration may plausibly be ascribed to various factors, and need not necessarily be related to the x-ray examination. In Cases 1 and 3, for example, the disease had been progressive, so that the condition of the patient might well have deteriorated apart from the puncture and injection.

No direct relation was observed between the angiographic examination and the deterioration. The changes in the patient's condition were not noticed until two to five hours after the injection. This may, however, have been due to the patient's not being observed sufficiently closely immediately after the examination.

If cerebral angiography is suspected to have been a factor in the deterioration, and it probably was, one might reason as follows :

In Case 1, in which thrombosis of the internal carotid artery was diagnosed, it is feasible that parts of the thrombus were torn off in association with the puncture and injection, and carried intracranially by the blood stream into the vascular twigs as emboli. Experience from other cases of thrombosis of the carotid artery and other vascular regions, however, argue against this theory.

In all three cases it is feasible that a vascular disease (definitely present in Cases 1 and 2) or compression of the vessel (Case 1) severely impaired the supply of blood to some parts of the brain, and that the fall in blood pressure and the vasoconstriction regularly following the injection of the contrast medium was sufficient to cause the decompensated circulation in the parts concerned to fail altogether. This explanation is, however, improbable, because with the widespread use of these contrast media in various conditions and in cases with well-established vascular changes, such complications would surely be more common. Nevertheless, the explanation cannot be excluded.

In all three cases the injection was rapid and the contrast media of high concentration. In two cases two injections of 50 per cent. contrast solution were given in rapid succession, and in the other case an injection of 35 per cent. contrast solution was followed by a 50 per cent. solution. The opacity of the vessels in the angiograms indicated that the concentration of the contrast substance in the cerebral vessels was high, and judging by the serial radiographs made at timed intervals the circulation within the region supplied by the internal carotid artery was slowed down in Cases 1 and 2, especially in Case 1. In these two cases the application time of the medium, that is, the time the contrast medium was in contact with the vessel wall, was longer than usual. This prolonged application time may give rise to the assumption that the post-examination deterioration of these patients was due to aggravation of a disorder of the vascular permeability.

In this connexion it would not perhaps be out of place to mention that Broman and Olsson (1948) have demonstrated in experimental animals that contrast media of the Diodrast type are capable of impairing the vascular permeability of the cerebral

vessels, that is, of breaking down the blood-brain-barrier, if they are of sufficient concentration and allowed to act upon the vessel wall for a sufficient length of time. In the cat and the rabbit the application time necessary for Umbradil Forte (50 per cent.) to impair the permeability of the cerebral vessels was found to be 5 to 10 seconds. Present investigations seem to indicate that in ischaemia, for example, a lesion may arise in spite of a very short injection time, owing to the fact that the application time is prolonged considerably by the decelerated circulation.

These investigations, based directly on the experience gained from clinical cerebral angiography, argue strongly in favour of the view that in the above-mentioned case the deterioration was due to a disorder of the permeability of the cerebral vessels on account of the contrast medium used. The clinical picture of these cases might well be explained by such a disorder. The changes were slightest and of shortest duration in Case 2, in which also the application time was the shortest and the injection the smallest.

It has also been demonstrated in animals (Broman and Olsson, 1949) that the injurious effect of contrast media of the Diodrast group varies according to the chemical composition of the contrast media, and, strangely enough, also according to the source of supply of media of one and the same composition.

Of the substances tested (Diodrast (Winthrop), Ioduron (Cilag), Dijodon (Leo), Umbradil, Umbradil Forte, and Umbradil-methyl-glycamine (Astra)), the widest margin of safety was provided by the use of Umbradil (35 per cent.), this substance producing no manifest effect on the vessel wall even after so long an application time as 40 seconds. Of the more concentrated contrast solutions, Umbradil Forte proved less injurious than any of the others. In less serious cases the injury passed off within two hours. These animal experiments show that the objections to contrast media of the Diodrast type may be overcome by choosing those substances which, in the pharmacologic tests described above, proved least injurious, and by applying as low a concentration as circumstances permit. If the injection is made into the internal carotid artery, a 35 per cent. solution will always give sufficient radiopacity. If the substance is injected into the common carotid artery, this concentration will almost always allow satisfactory angiograms to be made. Should a 50 per cent. contrast solution occasionally be considered necessary, the patient should be given but a single dose, which should be injected relatively slowly.

In view of the complications liable to supervene immediately after the administration of these

contrast media, and as hypersensitivity can never be definitely excluded, an urgent need for cerebral angiography must occasionally be assessed in the light of the risks involved.

From the above observations it will be obvious that difficulties encountered in cerebral angiography may make severe demands on the examiner, just as the interpretation and critical evaluation of the x-ray finding taxes the knowledge and experience of the radiologist. It would seem advisable to assign the use of this method to departments in which there is enough material available for the radiologist to gain experience in cerebral angiography. Examinations, of course, have to be planned, and the results evaluated jointly, by the radiologist and the clinician concerned.

Summary

The tolerance for contrast media of the Diodrast type was studied in three hundred and thirty cerebral angiographic examinations.

Sixteen cases reacted with a slight rise of temperature, two with severe allergic symptoms, and three with cerebral symptoms. These reactions are discussed, and the symptoms of the last-mentioned group are ascribed to a disorder of vascular permeability caused by the contrast medium.

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