Local Petechial Reactions Following Cerebral Angiography with Hypaque*

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Since the advent of the use of Hypaque Sodium 50 per cent (sodium diatrizoate) for cerebral angiography in 1956, there has been only cursory mention of local petechial reaction as a complication. Dunn et al.8 described the occurrence of homolateral petechial hemorrhages of the face, neck and conjunctiva on the side of injection in 1 patient. DeSaussure and Keirns7 noted a similar reaction in 3 patients in their reported series of 300 cerebral angiograms using Hypaque 50 per cent. In both of these reports the petechial reaction was mentioned only in passing and these constituted the only specified instances found in the literature of this untoward complication with this contrast medium in cerebral angiography. Personal communications8,9,13 have brought 7 other similar cases to our attention.

This report is concerned with the occurrence of local petechial reactions following cerebral angiography with Hypaque 50 per cent in 4 patients over a brief period of time at the Yale-New Haven Medical Center.

Case Reports

Case 1. A 19-year-old white female college student with no history of allergies entered the Grace-New Haven Community Hospital on Nov. 18, 1962, for investigation of left-sided paresthesias following a severe retro-orbital headache of several hours' duration.

History, physical examination and electroencephalogram indicated a focal cerebral lesion in the right parietal area. Cerebrospinal fluid was within normal limits.

On the 2nd hospital day, right cerebral angiography was performed using Hypaque 50 per cent. A total of 4 injections of 8 cc. each of the right common carotid artery were made to complete the studies.

Approximately 3 to 4 hrs. following arteriography, a petechial rash developed over the right side of the face (Fig. 1) which increased in intensity during the next 12 to 18 hrs., eventually involving the right side of the face, neck and palate to a marked degree, with less petechiae over the right upper chest and upper arm. The optic fundi were free of petechiae, although the conjunctiva was involved. The reaction reached its maximum intensity within 24 hrs. following onset, and began disappearing in 48 hrs. with complete resolution in 8 days.

There was no pruritis, fever, or change in neurologic signs or symptoms during the development of the reaction. Blood count and urinalysis were unchanged from the time of admission, and count of platelets was 175,000/mm². Capillary fragility test and petechiometer test at 20 mm. of mercury both gave negative results. Benadryl was instituted as an empirical therapy. A dermatologic

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consultant was of the opinion, however, that the reaction did not represent an allergic manifestation.

**Case 2.** A 50-year-old white widowed female entered the hospital for the 1st time on Nov. 27, 1962, with signs and symptoms of a right oculomotor palsy of 7 days’ duration. The patient had a past history of a transient weakness of the left leg, mild hypertension, and some questionable syncopal episodes. No history of allergy was elicited.

General physical findings were unremarkable except for a blood pressure of 230/120.

Neurologic abnormalities were a complete paralysis of the extraocular muscles supplied by the right oculomotor nerve with lateral deviation of the eye at rest, complete ptosis and fixed dilated pupil. Other findings were a mild weakness of the left lower extremity and a suggestive plantar extensor response on the left.

Bilateral carotid angiography was performed via percutaneous puncture of the common carotid arteries, using Hypaque 50 per cent. A total of 3 injections of 8 cc. each were made on the right side and 2 injections of 8 cc. each on the left. A large saccular aneurysm was present on the right internal carotid artery at the junction with the posterior communicating artery. There was also a fusiform dilatation of the left internal carotid artery in its intracranial portion.

Within 4 hrs. after angiography, a petechial rash developed over both sides of the face and neck, including the pharyngeal mucosa. Initially, the lips, buccal mucosa and conjunctivae were spared but became involved within the ensuing 24 hrs. There were no petechiae over the chest or arms, the rash being demarcated at the base of the neck. About 48 hrs. after onset, the petechiae began disappearing in a progressive manner. On the 10th hospital day (6 days postangiography) the patient suddenly died.

Autopsy revealed the cause of death to be rupture of the aneurysm of the right posterior communicating artery. There were also multiple small aneurysms bilaterally in addition to the fusiform dilatation of the left internal carotid artery noted at angiography. No cerebral petechiae were noted.

**Case 3.** A 24-year-old white man was admitted to the hospital on Dec. 3, 1962 for evaluation of post-traumatic headaches.

Four weeks previously, the patient had been involved in an automobile accident, at which he was rendered unconscious for an undetermined length of time. Since that time he had complained of left-sided frontal headaches which were associated with vomiting.

The patient was a poorly controlled diabetic with a moderate peripheral neuropathy, for which he had been followed in Neurology Clinic. There was no history of allergy.

Physical examination revealed signs of a distal peripheral neuropathy in the lower extremities.

Roentgenograms of the skull demonstrated a small osteolytic lesion in the left frontoparietal region. Electroencephalogram showed a left temporal slow-wave abnormality.

On the 1st hospital day, left cerebral angiography was performed by percutaneous injection of the common carotid artery with Hypaque 50 per cent. Two injections of 8 cc. each and 1 of 5 cc. were made. The study was normal. Approximately 4 hrs. following the procedure, a petechial reaction involving the left side of the face, neck and scalp developed. The retina and oral pharynx were free of petechiae. Coincident with this reaction was an elevation of temperature to 101°F and development of slight tender lymph-node enlargement in the left postauricular and occipital regions.

The fever subsided within 24 hrs. Both petechiae and lymphadenopathy had begun disappearing by the time of hospital discharge 2 days following angiography.

**Case 4.** A 44-year-old man with no history of allergies was admitted to the Neurology Service of an affiliated hospital on Jan. 7, 1963, with a chief complaint of severe headache for several hours.

Examination disclosed a right Babinski’s sign. Cerebrospinal fluid was grossly bloody with an opening pressure of 270 mm. of saline. One week following admission, bilateral carotid angiography, using Hypaque 50 per cent, was performed. Three injections of 8 cc. each were made into the left common carotid artery while 2 injections of 8 cc. each were made on the right side. A large aneurysm of the anterior communicating artery, which filled from the left side, was revealed. Four hrs. later, a massive petechial reaction was observed on the left side of the face and neck, including the conjunctiva. There were a few scattered, barely visible, petechiae on the right side of the face and neck but not in the conjunctiva.

Neurologic findings were unchanged from the pre-angiographic status.

On the following day, the patient underwent a craniotomy for ligation of the aneurysm. No petechiae were seen on the surface of the brain that was exposed during surgery. The cutaneous petechial reaction subsided completely over a 4-day period.

**Discussion**

It will be noted from the case histories of the Grace-New Haven Community Hospital that 3 reactions occurred in a 2-week interval. During that time, only 4 cerebral angiograms were performed on the University Service of the hospital. Hypaque 50 per cent had been used on the University Service
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for cerebral angiography for approximately 7 years without a similar documented reaction. After the third reaction, the entire remaining batch of contrast medium was returned to the manufacturer for analysis.

The manufacturer of the medium, Winthrop Laboratories, kindly provided us with information they received from another source concerning 2 patients in whom massive showers of petechiae developed following the introduction of Hypaque 50 per cent through an arterial catheter for vertebral arteriography. The petechiae were distributed in the skin corresponding to the distribution of the brachial and other arteries arising about the region of the tip of the catheter, and started to appear 1 to 2 hours after the procedure. It is of interest that these two reactions occurred in a brief interval without any prior similar experience by the physician concerned.

Personal communication with the authors who reported three petechial reactions in a series of 300 cerebral angiograms revealed that their reactions occurred within the first hundred procedures but did not occur consecutively. Bilateral petechial reactions following bilateral carotid angiography were described in a case report recently but there was no mention of the contrast medium used. We have since learned by personal communication that the contrast medium was Hypaque 50 per cent.

Recently, it came to our attention that Dr. M. Mishkin of the Radiology Department of the University of Pennsylvania had a similar experience. In the course of 12 hours he experienced 4 petechial reactions similar to ours following the use of Hypaque 50 per cent for cerebral angiography. In 1 of his patients a central scotoma developed which improved but was still present when last examined. Shortly thereafter he witnessed similar reactions with two other iodinated contrast media from different manufacturers. At the present time he has no additional evidence for determining the etiology of the reaction.

In all the reported cases, the reaction appeared within a cutaneous distribution in the supply of the injected artery, its branches and sometimes its immediate precursors. The reaction did not cross the midline in the unilateral angiograms. The skin bordering the site of injection, the ipsilateral face and conjunctiva were the most heavily involved sites.

Although a petechial reaction was produced experimentally in the cerebral hemisphere of a cat following a carotid injection of Hypaque 50 per cent, there are both morphological and clinical indications that the reaction we witnessed does not involve the brain. One patient reported elsewhere died while cutaneous petechiae were still present and postmortem examination revealed no cerebral petechiae. In Case 4 of this series, a craniotomy was performed for ligation of the aneurysm, 2 days following angiography, while cutaneous petechiae were still evident. No petechiae were present on the surface of the brain that could be visualized during operation. Similarly, no petechiae were seen in the postmortem examination of the brain in Case 2. In Case 1, a postangiographic electroencephalogram was not significantly different from that prior to the contrast study. Petechiae were never seen in the optic fundi and no patient manifested signs of ipsilateral cerebral dysfunction that might be expected if the hemisphere also was involved.

All 4 patients had angiography performed by the same physician without variation in technique among these and a number of uncomplicated cerebral angiograms previously and since. Investigation of the central supply department of the Grace-New Haven Community Hospital revealed that, surrounding the time of the three reactions, there was absolutely no change in technique of sterilization, detergents used for cleaning glassware, or personnel.

The reaction reported by Dunn et al. occurred in a patient with an allergic history. However, none of our patients had an allergic background.

Although Cases 1 and 2 received parenteral Benadryl when the reaction appeared in the skin, no medication was used to treat the latter 2 patients, and it appears that the course of the reaction was not altered by the use of the antihistamine.
Experimental studies have been performed with other iodinated contrast media and have shown that these media are capable of injuring the cerebral vessels of laboratory animals. This was manifest in an increase in permeability of the cerebral vessels and characterized by edema, stasis and punctate hemorrhages. It was observed that the incidence and the degree of severity of the vascular lesions varied according to the concentration of the medium used and to the duration of the application; that is, the time the medium was allowed to act upon the cerebral vessels. These experimental studies may indicate the mechanism for the petechial reaction that we have observed in our cases; however, this is only speculation and further experimental studies with Hypaque will be required before the mechanism can be elucidated further. Other possibilities suggested for the mechanism other than a direct irritant effect of high concentration of iodine in the vessels are 1) that reflex vasospasm occurred upon injection of the bolus of contrast material which on later vasodilatation caused capillary damage, or 2) that the petechial reaction may be related somehow to an impurity in the particular batch of contrast medium. The latter suggestion really is not substantiated in the cases in the literature or in our cases. Furthermore, an analysis of the returned supply of the material in question to Winthrop Laboratory did not reveal any irregularities.

It is interesting that Mishkin* experienced petechial reactions with other contrast media shortly after the Hypaque reactions. This suggests that something other than the contrast medium is the causative factor. As mentioned earlier, investigation of these possibilities in our institution did not prove fruitful.

Reports describing petechial reactions following the use of other contrast media for cerebral angiography were also unexplained as to mechanism.1,12

Although we can offer no explanation of the mechanism of this reaction, it appears to be an unusual, unpredictable, benign, and self-limited mucocutaneous phenomenon.

(Shortly before submission of this report for publication, 2 additional cases of petechial reactions following carotid arteriograms using Hypaque 50 per cent occurred consecutively at this institution. The studies were performed by different physicians and the reactions were completely analogous to our 4 described cases.)

Summary

The occurrence of local mucocutaneous petechial reactions following cerebral angiography using Hypaque Sodium 50 per cent was described and discussed together with a review of the literature. The complication is a benign and self-limited reaction which is probably a localized effect on blood vessels of an as yet unexplained mechanism.

References

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