CALCIUM IN EPILEPSY

By

GWENVRON M. GRIFFITHS, LINGFIELD EPILEPTIC COLONY

INTRODUCTION

THE possibility that the epileptic crisis may be associated with some disturbance of calcium metabolism has attracted many workers. My attention to the problem was aroused by an accidental observation in a girl of nine years old, who had cycles of 60 to 100 fits monthly for three or four months, and was then comparatively free for a similar period. Towards the end of one of the fit-cycles she was asthenic and dull, and her ribs had become so soft that they were bent out of shape by the pressure of her arm as she lay in bed. She showed the signs of Chvostek and Trousseau, but had no other symptoms of tetany. Unfortunately, the serum calcium was not examined at this time. As she became stronger after the end of the fit period the softness of the ribs and the deformity disappeared.

Investigations of the serum calcium content in epileptics have been made by several workers, and the findings have usually shown it to be within normal limits or at the lower level of normal values. Lennox and Allen, making single observations on 77 epileptics, found an average of 9.79 mg. per 100 c.cm. of serum, as against a normal average of 10.067 mg. Parhon and Ornstein in 85 cases found values at or below the lower limit of normal, which they considered to range from 10 to 12 mg. per cent., only two of their cases showing higher values. Madsen, with repeated determinations on a group of patients, found an average of 10.4, as against a normal average of 10.8 mg. per cent., but he noted a very much wider range of variability. His figures showed marked individual variability also. He has given details of the relation of his findings to fits in some cases, showing mostly high values before and during runs of fits, and a low value after a run of fits, but he does not state the times of the fits. He found the Ca/Na ratio normal, but excess of Ca in the Ca/K ratio. Hamilton, in his study of the inorganic constituents, found in 19 estimations that the serum calcium ranged from 9.6 to 12.8 mg., and the phosphorus from 2.6 to 6 mg. Osnato and Killian, in a similar study, found in 19 estimations serum calcium values from 9.5 to 12.8 mg., with an average of 10.9 mg., and phosphorus values in 11 cases from 2.5 to 4.5 mg. Other workers have considered the question of the ionic state of the calcium, calculating the free ions from the pH of the blood and the alkaline reserve. Bigwood, in several studies, has found a rise of alkalinity and a consequent fall in calcium ions preceding a fit. Di Renzo, however,

by similar methods found a rise of alkaline reserve till an hour before a fit, then a sudden fall, suggesting an increase of calcium ions preceding the attack.

Many of these findings are not harmonious, and additional information that would be relevant is meagre or absent. While details are given in some cases, the time of the fit is not recorded, nor is the relationship of the fit to other attacks. In several cases only interparoxysmal estimations are recorded. Also, much of the work has been done on chronic institutional cases.

Several investigators have reported the results of calcium treatment by mouth or intravenously. Petzetakis was convinced of the great improvement in two cases treated with intravenous calcium chloride, which he found to inhibit the fit. Klein and Forcione found no improvement, but rather a tendency to increase of fits in cases treated by intravenous calcium, though in their cases luminal had been discontinued for the period of the experiment. Hopkins Detrick considered that calcium treatment reinforced by methods for raising the calcium content of the blood was of value in all types of cases.

PERSONAL STUDIES

It seemed to be worth while to make a fairly large number of repeated observations of serum calcium on a group of young epileptics, who were living a normal school and out-door life on a colony. Samples of blood were taken at various times of the day and at varying intervals over a prolonged period, in the hope of obtaining a sufficient number of observations to be able to correlate them with the time of the fits, which are all recorded in detail as a routine. The cases chosen were nearly all those of young males from 10 to 25 years old, not mentally defective, and with various types of fit and fit incidence. There was no change in their routine or diet except for occasional experiment. The chief difficulty was to obtain samples of blood immediately before a seizure or group of seizures; in 540 estimations only one was less than five minutes before the fit. There was also difficulty in obtaining the samples in relation to fits occurring at night; when blood was taken during the night the subjects had no fits.

The estimations were made on 48 individuals, two only being girls, on whom six observations were made. The method used was that of Kramer and Tisdall, with, as a rule, 2 c.cm. of serum. Duplicate estimations were frequently done, with a difference of never more than 0.2 mg. in the result. The estimations were all carried out by the same person and as far as possible under the same conditions, at least eight being done in a batch. Some 433 estimations were made on serum separated from the clot after standing overnight; in the remaining 108 the serum was expressed by immediate centrifuging, so that estimations of serum phosphorus might be made on the same sample. As a control 16 samples were split, and half centrifuged immediately

and the rest left to clot overnight. Of these, in nine cases the value obtained from the serum from overnight was higher than that found by immediate separation, in three cases lower, and in four about the same. The average values obtained from the immediately separated sera were found to be about 0.5 mg. lower than those from sera obtained by standing, and the range of values wider, and the former values have therefore all been ignored in the results now to be recorded.

From a total of 433 estimations of serum calcium an average reading of 10.126 mg. per 100 c.cm. was obtained. This lies within the normal limits of 9.5 to 11 mg., and agrees fairly closely with the findings of other observers. The range of values, however, was found to be wide, as shown in the appended table.

TABLE I. RANGE OF SERUM CALCIUM

Between 6 and 7 mg.	3 cases	0.7 per cent.
7 8	7	1.62
8 9	40	9.47
9 10	123	28.41
10 11	166	38.33
11 12	79	18.24
12 13	13	3.33
13 14	1	0.23

The majority of readings are within the normal range. The variability in range is found in individuals as well as in the whole group. In 22 subjects the range was small, within the limits of 2 mg. per 100 c.c.; in six of these the values lay wholly below 10 mg., while in four the range was wholly above this figure. In 17 individuals the variation is much greater. I could find no correlation between the range of values and the frequency or type of fit.

In correlating the serum calcium findings with the occurrence of seizures, it was found impossible to make a constant correspondence in individual cases, but by averaging the readings some correlation appeared when considering major fits only.

TABLE II. CORRELATION OF VALUES WITH FITS

Fit-free interval	205 readings	average 10.032 mg.
Within 48 hours before fit	87	10.162
Within 48 hours after fit	102	10.056
Between two fits, within 48 hours of either	39	10.718

In this table we see that the average value before fits is slightly but definitely higher than after the seizures. The highest figure, obtained between fits at close intervals or during a series, is striking and unexpected. Actually, in 23 of the 39 values so obtained, the figure was over 10·5 mg., and in several cases over 12 mg. In two cases, however, when blood was taken during a series of fits which proved fatal—one in a girl and one in a boy—the values were 8·8 and 8 mg. respectively, in marked contrast to the other findings. Readings after a run of fits proved to be low in many cases; values from 6·2 to 8·8 mg. were obtained from seven cases under these circumstances.

An attempt was made to correlate the serum calcium findings with the usual time of the fit in individual cases. The subjects were divided into groups of (1) those with fits by day or by night only, (2) those with fits either by day or night, and (3) those who tend also to have fits during the waking period (taken as from 6 to 7 a.m.). The results are given in Table III.

TABLE III. RELATION OF CALCIUM WITH USUAL TIME OF FIT

Group by time of fit	Fit-free interval	Average 48—24 hours before fit	Average 24 hours—time of fit	Average up to 24 hours after fit	Average 24—48 hours after fit	Between two fits
Day only (15 cases)	10·06	9·74	10·12	9·74	10·55	11·3
Night only (14 cases)	10·07	10·08	10·33	9·83	10·3	10·5
Day and on rising (6 cases)	9·74	10·56	9·95	10·21	10·4	11·3
Night and on rising (5 cases)	10·14	10·32	9·76	10·31	10·35	10·24
Mixed day and night (8 cases)	10·09	10·37	10·15	10·17	10·48	10·3

In this table the very close correspondence of the values in the fit-free interval is noticeable. The groups who have fits at the rising hour show a reversed behaviour of the calcium before and after fits as compared with the groups who do not have fits at these times, the postparoxysmal values being higher than those before fits instead of lower as in the other groups. No regard of the actual time of the fit was taken in making this correlation. Where, however, the figures for each hourly interval before and after fits are examined, a definite difference in the behaviour of the serum calcium is disclosed according as the fit occurs during the day or the night. Figures for the rising hour were insufficient to warrant any conclusion, while in the hourly series some inevitable blanks occur. With fits during the day the average values from 48 to 20 hours before the attacks are high; then, till about four hours before, they are definitely lower; then there is another rise till

during the last hour before the fit there is a drop of 1 mg. in the average figure; this lower value is maintained during the hour following the fit, followed by a period of high values for about 14 hours, then relatively low values till a 'normal' level is reached about 36 hours after. When the fits occur during the night, however, the periods of low and high values appear to be almost completely reversed, but I have no figures nearer than three hours from the paroxysm. In Chart I this curve is shown with averages calculated for six-hourly periods.

The actual values obtained within one hour of a fit, occurring during the day, are given below.

TABLE IV. ACTUAL CALCIUM VALUES WITHIN ONE HOUR OF A FIT

45 minutes before a major fit	12 mg. (in a series)
4 minutes before	6.8
Fit occurring while blood taken	10 (in a long series)
	9.4 " "
10 minutes after fit	10.8
	11.9
	8.8 (in a fatal series)
30 minutes after	10.5
	8.5 (a case with low Ca)
50 minutes after	10.2
	11.4 (in a group)
	10
	9.6

In one case of special interest the readings obtained in the free intervals were unusually constant, the value on six occasions being 9.4 mg. In this case, 27 hours after a group of fits arising during the day, a value of 7.4 mg. was obtained. A reading of 10.4 mg. was obtained three hours after a fit in a group starting at night; and on three occasions, 10 to 40 hours after groups of fits during the night, the relatively high values of 10.4, 10.7 and 10.3 were found. This case strongly suggests that there is some metabolic difference between fits occurring in the daytime and those that occur at night.

A few estimations were taken between 1 and 2 a.m., when the patients were asleep. In four cases readings were low (8.4 to 8.8 mg.), and in two of these, fits occurred during the following night. In four other cases readings were 9.4, 9.8, 10.1 and 11 mg. In the last case a fit occurred at 6.5 a.m., 28 hours after the blood had been taken.

CHART I.—Serum Calcium Averages Before and After Fits. Six-hourly Averages.

The influence of the drugs taken as routine treatment was noted. There is not much difference, but the group having luminal showed slightly higher average values than those who were not on this drug.

TABLE V. INFLUENCE OF DRUGS ON CALCIUM CONTENT

On luminal	15 cases	average Ca 10·16 mg.
bromide	8	9·98
luminal and bromide	9	10·01
other drugs	10	10·07

The effect of intensive calcium treatment, and of diminution of the serum calcium, was studied in certain cases. Eight patients who tended to have a low calcium level were given one drachm of calcium gluconate by mouth three times a day, two drachms of cod liver oil and a pint of milk daily, in addition to their normal diet, for a period of four months or more. Of these, five showed an increased level of serum calcium, which, however, was erratic and ill-sustained. In two cases there was a slight increase of fit incidence, in two there was no change, and in the other there was some degree of improvement. In two of these cases an increase of fits followed the cessation of the calcium treatment. In one of the cases the improvement was very marked. This patient had for many years had repeated and severe attacks of status epilepticus as well as isolated fits. During the three years preceding the investigation he had had 22, 15 and 19 status attacks respectively, and during the first three months of 1932, 10 attacks. Calcium gluconate intravenously had been given in four of these, with immediate results on two occasions. In April, 1932, he was put on the calcium régime. Since then there have been only five status attacks during 20 months, though there has been no reduction of the isolated fits. Another patient was started on calcium treatment after an attack of acute tetany. Blood taken during the attack, which was stopped by intravenous calcium, showed a serum calcium value of 10·7 mg., but subsequently he had on several occasions lower values of 7·7 to 8·4 mg., unconnected with fits. In fact, for six months he had no fits, though this should probably be attributed to luminal rather than calcium.

Five patients who tended to have a high calcium level were given sodium sesquiphosphate in doses of 10 grains three times a day. In three cases the calcium level was markedly reduced, while in all the cases there was an increase in the number of fits, the increase being persistent for two or three months after stopping the treatment. It appears, therefore, that while increase of calcium is not in itself sufficient to control the fits, a diminution of calcium is definitely detrimental.

SERUM PHOSPHORUS

On 70 occasions the serum phosphorus and calcium were estimated on the same sample of blood. For this purpose the blood was spun immediately, and the serum calcium values may therefore be inaccurate, though the

calcium phosphorus ratios obtained suggest that the error is not great. The average value obtained for phosphorus was 4.493 mg. per 100 c.cm., while the average calcium was 9.23 mg., rather lower than the average obtained when the clot is left overnight. The range for the phosphorus readings was from 1.8 to 11.4 mg.; in 46 cases it lay between 3 and 5 mg.

TABLE VI. CORRELATION OF PHOSPHORUS WITH MAJOR FITS

Fit-free interval	38 cases	average 4.31 mg.
Within 48 hours before fit	16	4.12
" " after	10	4.36
Between two fits, within 48 hours of either	6	3.73

These values for serum phosphorus agree with the findings for serum calcium shown earlier, the lower phosphorus before fits corresponding with the higher calcium, and vice versa.

The relationship between phosphorus and calcium does not seem to be consistently disturbed in connection with epileptic fits, as shown in the 'scatter' diagram (Chart II). Though most of the values outside the normal area (3 to 5 mg. phosphorus and 9 to 11 mg. calcium) are related to fits or to severe chilblains, an equal number of values within 48 hours of a seizure are within the normal.

SUMMARY

1. In a series of observations over a period of time on a limited number of cases, the average serum calcium is found to fall within normal limits, though the range of values is wide and variable, for the group and for individuals alike.

2. The average of values before a fit is found to be greater than that after a fit. The highest range of values is that obtained during a run of fits, while low values are found after a run. In two cases, estimations made during a run of fits which terminated fatally proved to have definitely low values.

3. When cases of fits by day are contrasted with those of fits by night, the averaged figures show that the behaviour of the serum calcium in relation to the attacks varies inversely in the two groups. This inversion is confirmed in a striking manner in one particular case, which gives low values after day fits, high values after night fits, and a persistent median value in fit-free intervals.

4. Treatment with large doses of calcium may have beneficial results, while the diminution of serum calcium by sesquiphosphates is definitely detrimental.

5. Serum phosphorus is found to be within normal limits, though with a wide range of variation. Its relation to the serum calcium is not always disturbed by fits, though abnormal ratios may be associated with attacks.

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