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Intracapsular Irradiation Therapy of Craniopharyngiomas with Radioactive Gold: Indication and Follow-up Results

Takafumi KODAMA, Yasuhiko MATSUKADO and Shozaburo UEMURA

Department of Neurosurgery, Kumamoto University Medical School, Kumamoto 860

Summary

Sixteen cases out of 27 patients with craniopharyngiomas were arbitrarily subjected to combined treatment of simple surgical evacuation and intracapsular irradiation with 198-Au. Follow-up studies were performed on 15 cases and they ranged from 6 months to 11 years. One patient was omitted from the study because of a short postoperative period. Immediate postoperative morbidity and the endocrine functions at the end of the follow-up study were compared with those of the patients who underwent extensive surgical resection of the tumors. Intracapsular irradiation with 198-Au was found to have satisfactory effects in the treatment of cystic craniopharyngioma, especially in recurrent cases of initially solid tumors, with respect to the preservation of the endocrine functions and the daily activity of the patients. The immediate postoperative hazards in the patients' care were also much less and they were found to be easily manageable. The patients, who had been followed up for over 5 years, maintained an occupational IQ score in the normal range and the patients under school age were all able to continue their school lives. One of the female patients, who had been married after the treatment, could have two children without any specific replacement therapy, and another patient in childhood who had shown physical retardation due to HGH deficiency, showed favorable results with crescormon administration in comparison with cases of extensive resection. Although the dosimetric value of 198-Au should be varied according to the size and thickness of the capsule, it was found that 15 to 30 mCi of 198-Au was the appropriate dosis for treatment.

Key words: Craniopharyngioma, radiotherapy, follow-up study, endocrine function, daily activity

Introduction

In reviewing the technical advances in neurosurgical operations, procedures which aim at radical treatment have been quite rewarding in most cases such as total resection of an acoustic schwannoma or clipping of an arterial aneurysm. Technical facilities have been widely promoting radical neurosurgical treatment and the surgical microscope has resulted in great achievements in recent years. However, a number of problems still remain which can not be solved by a simple "in toto" procedure. The surgical treatment of a craniopharyngioma is one of these problems since extensive resection of the tumor is apt to be followed by diversified endocrinological disturbances. The tumor can also recur frequently even after total resection in the initial operation, and this is another disputable feature of the treatment.

Although the histological findings of craniopharyngiomas indicate no malignancy, attempts to irradiate this well differentiated epithelial tumor were initially undertaken almost half a century ago by Carpenter[2], and radiation therapy was found encouraging by Ingraham[4], Love[8], Kramer[6] and others. Nevertheless, radiation therapy has also been the subject of criticism for many years simply because of the low sensitivity of neoplastic cells to radiation and the side effects on endocrinological functions. To avoid unnecessary radiation effects on the hypophyseohypothalamic system, intracapsular irradiation with 32-P in a sodium phosphate solution was first performed by Leksell[7] in 1950. By appropriate selection of radioactive isotopes, it was found that accumulation of the cystic content could be attenuated successfully without untoward effects on the surrounding structures. Up to the present several kinds of radioactive material have been employed, such as bismuth phosphate, chromic phosphate and yttrium, for intracapsular irradiation. Some of them were injected into the cyst utilizing the stereotaxic technique. In 1960, Bond[1] described his experience of irradiating cystic craniopharyngiomas with a small dosis of radioactive gold which is not only a β emitter but also a γ emitter. Clinicopathological examinations of the reported patients revealed that the appropriate dosis of 198-Au for intracapsular irradiation was 10 to 15 mCi. Although the dosimetric value of 198-Au should be varied according to the size and thickness of the capsule of the craniopharyngioma, intracapsular irradiation with 198-Au was found to have satisfactory effects in the treatment of cystic craniopharyngiomas, especially recurrent craniopharyngiomas, with respect to preserving endocrine functions. It is the purpose of this paper to report the favorable results of intracapsular irradiation with 198-Au which were observed in a follow-up study of 15 patients, and to discuss the therapeutic advantages and limitations of this method.

Clinical Materials and Methods

During the last 11 years, 27 cases of craniopharyngioma were surgically treated at the University Hospital and five of them were found to be an almost totally solid mass. The rest of the cases were cystic or partly cystic craniopharyngiomas and 16 of them were arbitrarily subjected to intracapsular irradiation with 198-Au colloid after simple surgical evacuation of the cyst. Follow-up studies were performed on 15 patients and they ranged from 6 months to 11 years. One patient was omitted from the study because the postoperative period was not longer than 6 months. Seven patients were females and the patients' age ranged from 3 to 47 years old. Three patients received intracapsular irradiation twice and one patient underwent a third injection of radioactive gold.

For the clinical evaluation, all of the patients received routine general physical and neurological examinations prior to treatment and in the follow-up period as often as possible. Endocrinological assays of the patients were also repeated prior to and after the surgery, and in the follow-up study as well although this was not feasible in all of the patients. Immediate postoperative morbidity of the patients who underwent intracapsular irradiation was compared with that of patients subjected to extensive resection of the tumors. Seven out of 15 patients were suffering from recurrent craniopharyngioma and two of these patients had undergone multiple craniotomies.

As the operative procedure, right frontotemporal free bone flap craniotomy was applied and aspiration of the cyst was performed. A small piece of the tumor capsule was resected for histological examination, but no further resection of the tumor was attempted unless it was indicated to decompress the bilateral optic nerve by means of partial resection of the tumor. The cystic cavity was carefully inspected to determine whether the cyst was multiloculated or not, and occasionally, the septal membrane in the cystic cavity had to be ruptured. The tube of Ommaya's reservoir was placed in the cyst at a sufficient length and the opening was closed tightly with the tube sutured to the capsule. The reservoir was usually placed in one of the anterior burr holes above the temporal muscle.

About one week after surgery when the craniotomy wound healed, a small amount of water soluble contrast media was injected through the reservoir into the cyst. The size and shape of the cyst were estimated with X-rays and the solid portion of the tumor was roughly outlined from the preoperative pneumogram or CT scan. According to the thickness of the capsule and the size of the tumor, 15 to 30 mCi of 198-Au colloid was injected into the cyst. The therapeutic effect of radioactive gold was evaluated by puncturing the reservoir and aspirating the cystic contents after the patient was discharged from the hospital. The color of the cystic contents appeared to be clearer whenever the aspiration was repeated and the volume also decreased if the intracapsular

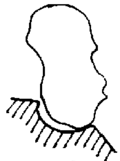
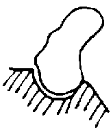
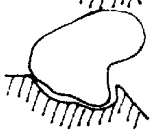
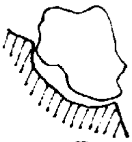
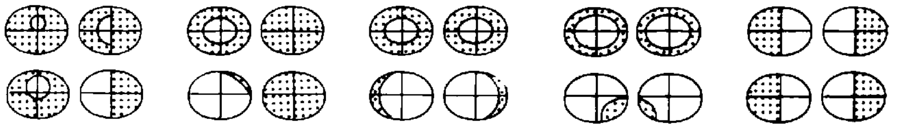
Case No:	Sex	Age Onset	Age Present	Treatment before intracystic irradiation	Calcification on plain film	Dosis of 198 Au	Dosis on the wall	Size of the tumor
1	M.	34	59	Partial excision. 5 times in 9 years.	–	15mCi	10,900 rads	
2	F.	12	24	partial excision. half a year before irradiation.	+	15mCi 20mCi 20mCi	80,500 rads	
3.	M.	20	36	partial excision. 4 and a half years before irradiation.	–	20mCi	21,800 rads	
4.	M.	9	28	partial excision. 3 and a half years before irradiation.	++	17mCi	48,200 rads	
5.	F.	14	25	Torkildsen's procedure	+	20mCi 26mCi	54,200 rads	
6.	F.	9	17	none	+	20mCi	77,800 rads	
7.	F.	22	29	none	–	17mCi 17mCi	104,200 rads	
8.	M.	16	24	none	+	20mCi 20mCi	188,300 rads	
9.	M.	3	7	partial removal. 2 times in 1 year.	–	20mCi	74,800 rads	
10.	M.	35	46	partial excision. 8 years before irradiation.	+++	30mCi	24,900 rads	
11.	M.	26	29	none	+	20mCi	66,000 rads	
12.	F.	16	22	none	+	20mCi	39,400 rads	
13.	M.	5	8	total excision. one year before irradiation.	+	20mCi	107,300 rads	
14.	F.	47	52	none	+	20mCi	12,900 rads	
15.	F.	8	11	none	–	20mCi	25,900 rads	

Fig. 1 Summary of the patient's history, radiological findings of the craniopharyngioma and the radiation dosis.

Case No:	1	2	3	4	5
Length of survival after initial symptoms	25y.	12y.	16y.	19y.	11y.
Period of follow-up after radiation therapy	11y.	9y.	8y.	7y.	6y.
Visual acuity					
preoperative	vd 0.05(0.1 × −2.0D). vs m.m	1.2(n.c) m.m.	0.2(n.c) 0.2(n.c)	0.5(1.0 × −0.5D) 0.1(0.2 × −1.5D)	0.1(0.3 × −1.0D) 0.5(n.c)
postoperative	vd 0.08(0.1 × −2.0D) vs m.m.	0.1p(1.0 × −2.5D) 0	1.5(n.c) 1.5(n.c)	0.2(0.8 × −1.0D) 0.5(0.8 × −0.5D)	0.08(0.1 × −2.0D) 0.2(n.c)
Visual field preoperative postoperative					
Replacement therapy	Prednisolone Thyroid sic.	Rinderone Thyroid sic.	none	Testinon	none
Occupation and daily activity					
preoperative	Policeman	student of junior high school	office clerk	factory worker	factory worker
postoperative	retired under the age limit	home life (full activity)	same as above	same as above	same as above

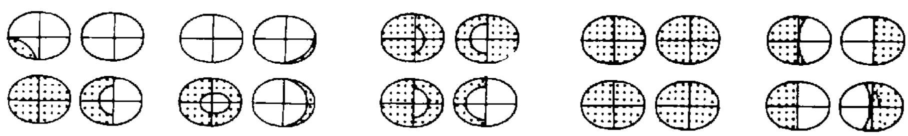
Case No:	6	7	8	9	10
Length of survival after initial symptoms	8y.	7y.	8y.	4y.	11y.
Period of follow-up after radiation therary	6y.	5y.	3y.	2y.	2y.
Visual acuity					
preoperative	vd 0.3p(n.c) vs n.d/15cm	1.0(n.c) 0.3(n.c)	1.2(n.c) 0.1(0.5 × −1.5D)	blindness	0.1(n.c) 0.5(n.c)
postoperative	vd 1.5(n.c) vs 1.0(n.c)	1.2(n.c) 1.0(n.c)	0.8(0.9 × −0.5D) 0.03(n.c)	blindness	m.m. 0.2(0.5 × −0.5D)
Visual field preoperative postoperative					
Replacement therapy	Crescormon	none	none	none	Rindren Thyroid sic.
Occupation and daily activity					
preoperative	high school student	housewife (mother)	farmer	housewife	farmer
postoperative	same as above	same as above	slightly limited activity due to visual disturbance	limited activity due to blindness	limited activity

Fig. 2 (*continued*)

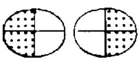
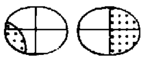
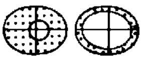
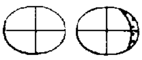
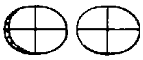
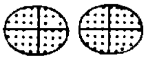
Case No:	11	12	13	14	15
Length of survival after initial symptoms	3y.	6y.	3y.	5y.	3y.
Period of follow-up after radiation therapy	1y.	1y.	9m.	7m.	6m.
Visual acuity					
preoperative	vd 0.03(n.c) vs 1.2	0.05(0.07 × −1.7D) 0.1(0.5 × −1.0D)	0.5(n.c) 0.01(n.c)	blindness	0.1(n.c) 1.5(n.c)
postoperative	vd 1.2 vs 1.2	0.1(n.c) 0.3(0.9 × −1.0D)		blindness	0.1(n.c) 1.2(n.c)
Visual field					
preoperative					
postoperative					
Replacement therapy	none	none	Crescormon	Rinderon Thyroid sic.	none
Occupation and daily activity					
preoperative	factory worker	home life (full activity)	school boy	housewife	school girl
postoperative	same as above	same as above	school boy	limited activity due to blindness	school girl

Fig. 2 Cumulative illustration of each patient in regard to visual functions and daily activity in the follow-up study.

irradiation had been sufficiently effective. On the contrary, cystic contents did not show any reduction in the color or volume when the intracapsular radiotherapy was not as effective as expected. For such cases, it was advised to repeat injections at another dosis or a slightly higer dose of radioactive gold. On the other hand, puncture or revision of the reservoir had to be performed immediately whenever it showed any tight bulging or obstruction, and eventually two patients underwent extensive partial resection of the tumor after irradiation therapy.

Results

The patients of this study are summarized in Fig. 1 in which the injected dosis of 198-Au colloid, estimated radiation dosis on the cystic wall and schematic size of the tumor are shown. Injections were performed a total of twenty times in 15 patients. One of the patients, case No. 2, received injections three times, but the first injection was considered less efficient because more than one third of the dosis disappeared into the subcutaneous tissue at the time of injection with no noticeable complications. Three patients received injections twice and one of them, case No. 5, underwent subtotal resection of the tumor after irradiation showed temporary improvement for a certain length of time. It was particularly interesting to find that resection of the residual tumor capsule was much easier than the initial operation, and isolation of the tumor from the surrounding structures was performed with minimal difficulty when the tumor capsule was enveloped with thin gliotic tissue. Eleven patients required only single injection and the results of follow-up studies were quite favorable except for case No. 10, which had undergone resection of the tumor with a calcified capsule.

Eleven out of 15 cases were able to resume their previous occupations with practically no difficulties and they were able to carry on their social or school lives normally.

Case No. 10, a farmer, was regaining his working capacity, although it was still somewhat limited due to general fatigue and memory disturbance because of sustained bitemporal hemianopsia. He had been on periodic replacement therapy with a corticosteroid and thyroid gland extract.

Three patients, case Nos. 8, 9 and 14, failed to show improvement of visual difficulties after treatment and their social activity was as severely limited as before the operation although two of them did not require any replacement medication.

Five patients who had been followed up for over 5 years received the WAIS test and the scores of their occupational IQ were all in the normal range.

The results of neuroophthalmological examinations before and after the intracapsular irradiation are illustrated in Fig. 2. Nine out of 15 patients showed improvement of their visual impairment in both acuity and the field, whereas four patients received no remarkable benefit from the treatment with respect to the visual difficulties and two patients showed progressive visual deterioration after a certain period of temporary improvement. The latter two patients were eventually subjected to subtotal or extensive partial resection of the tumor (case Nos. 5 and 10).

Endocrinological examinations of various kinds were performed during the follow-up study and the results can be summarized as follows: Figure 3 shows the plasma cortisol level before and after the intracapsular irradiation. The level of plasma cortisol was very low and the response to hypoglycemic stress in the insulin tolerance test was not sufficient in almost all cases. The data were compared with those of patients who underwent surgical resection of the tumor but did not receive intracapsular irradiation. As shown in Fig. 3 the intracapsular irradiation did not cause an additional fall of the plasma cortisol level when compared with the data obtained before the treatment as well as the data from cases of extensive surgical resection. HGH values are shown in the same figure, and they were also negligible in most of the patients before treatment. However, the values of case Nos. 3, 4, and 7 indicated a promising response to the insulin test in the follow-up study. From these data, the low value of plasma cortisol and HGH can be attributed to the ill effects of the tumor itself but not to the intracapsular irradiation. Crescormon, the human growth hormone, was administered to two physically retarded children because of HGH deficiency (case Nos. 6 and 13). Figure 4 shows the response of physical growth observed in case No. 6, which received intracapsular irradiation at the age of 9 and crescormon at 12 and a half. The response was compared with the standard

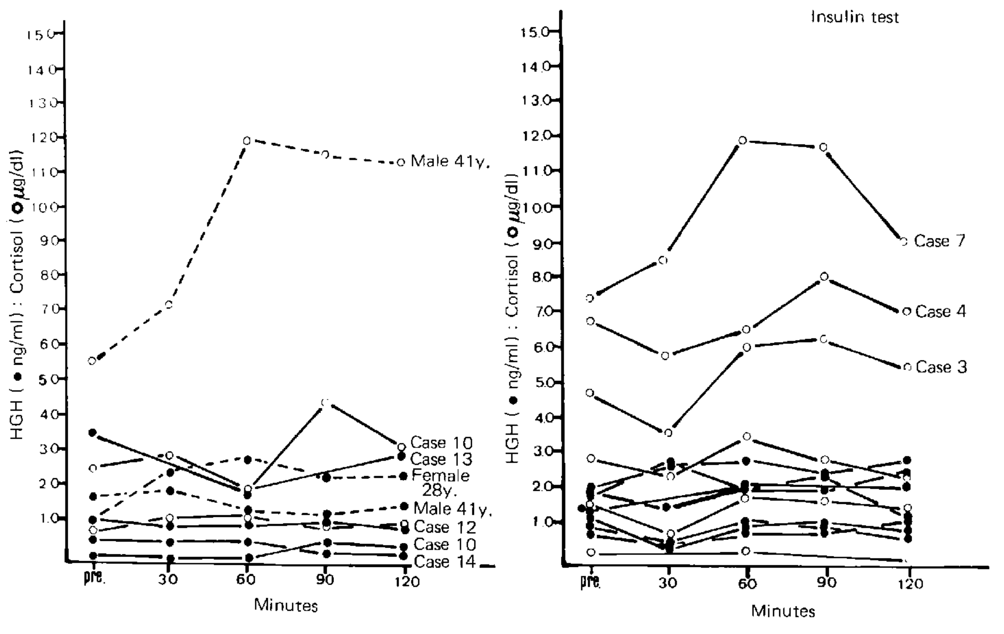


Fig. 3 Plasma cortisol and HGH, and the results of the insulin test, before (left) and after (right) intracapsular irradiation. The data were compared with those of cases of extensive surgical resection which are listed on the left without case numbers.

growth curve and the curve observed in the other child who underwent total excision of the tumor. At present the patient is 17 years of age and her physical height is still less than average,

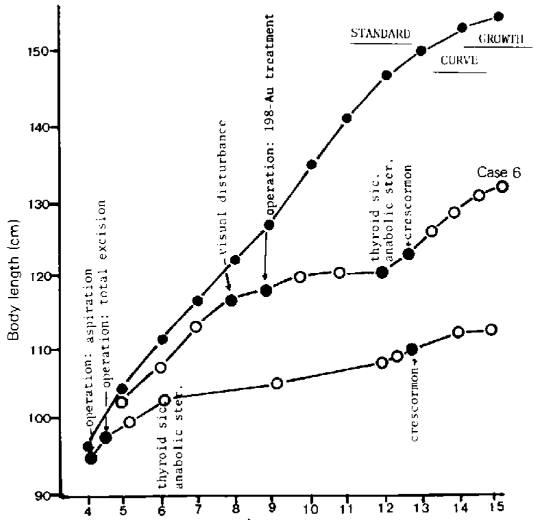


Fig. 4 The response of physical growth to crescormon (human growth hormone) in case No. 6. The data were compared with the standard growth curve and that of a child who underwent total excision.

but fairly satisfactory physical growth is expected. On the other hand, the response of the other child in the same figure appeared less promising although surgery was performed in early childhood and crescormon was administered 8 years after total excision. This result could be evidence indicating the disadvantage of extensive surgical resection of the tumor in the case of impaired HGH secretion.

Plasma TSH levels of the patients are shown in Fig. 5 and they are compared with the data obtained before radiation and the data of three patients who underwent surgical excision only. At the end of the follow-up study the TSH value of two patients remained at the lowest level and responded insignificantly to the TRH test, but the rest of the patients appeared to have subnormal or fairly good responses. Again, it can be said that the intracapsular irradiation should not cause any additional damage to the endocrinological functions.

Figure 6 shows the plasma PRL level in the same manner as before. In most of the cases the value was at the lowest level in the follow-up study and the response to the TRH test was quite similar as indicated by case No. 15.

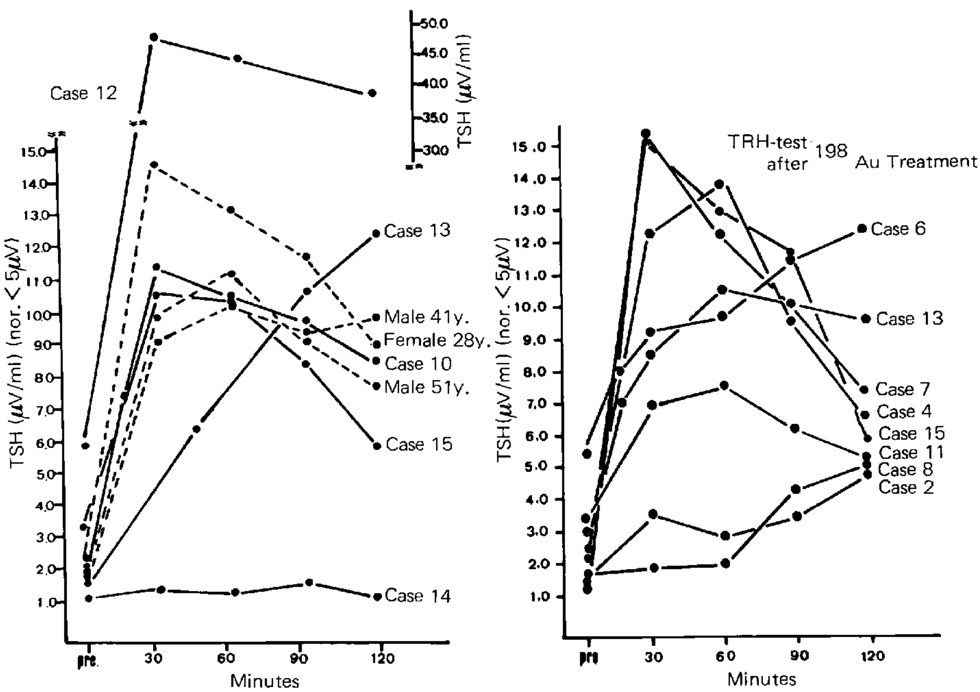


Fig. 5 Plasma TSH and the response to TRH before (left) and after (right) intracapsular irradiation. The data were also compared with those for three other patients of radical excision.

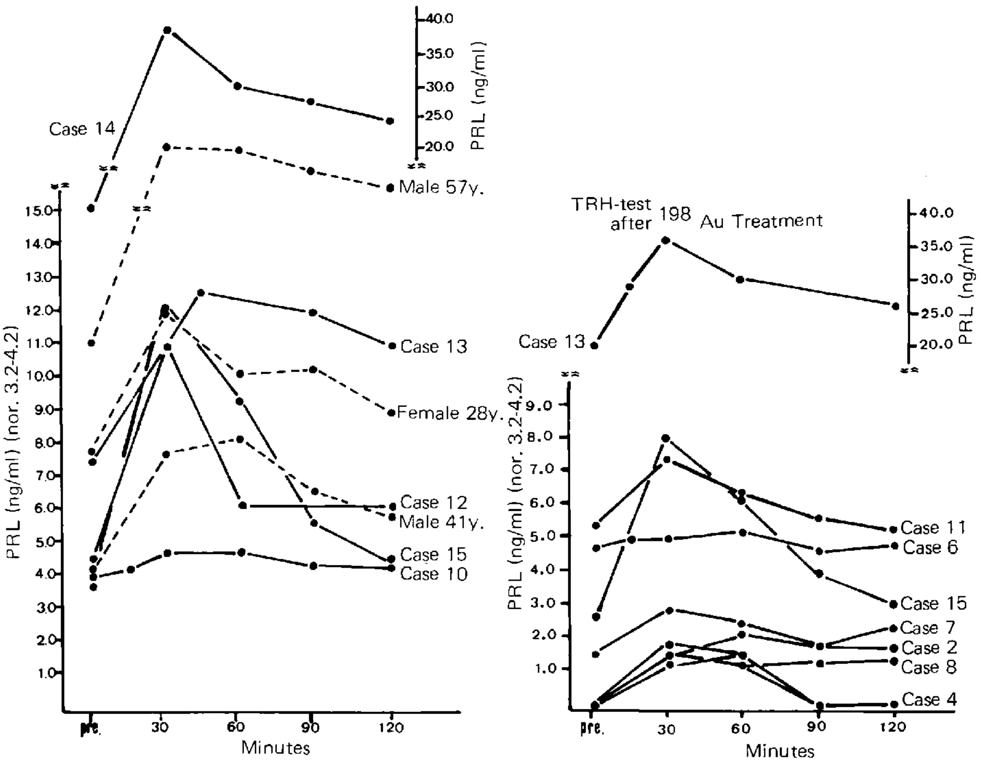


Fig. 6 Plasma PRL illustrated in the same manner.

One case, No. 13, showed an increased PRL value after intracapsular irradiation. The patient underwent total excision of the tumor one year prior to the intracapsular irradiation and the tumor recurred. The PRL value had been above the normal level and the response to the TRH test indicated a possible hypothalamic dysfunction which appeared to be more conspicuous after the treatment.

Plasma LH and FSH levels were found to be almost negligible in all of the patients and there was no noteworthy difference in the pre- and post-irradiation values, as well as those in cases of surgical excision only. However, the authors are particularly grateful to have a patient (case No. 7), who has become the mother of two children 5 years after the intracapsular irradiation. She was not on any replacement therapy when she became pregnant and had no difficulty in delivering the babies.

Plasma T3 and T4 levels were estimated as normal or slightly below the normal range.

Discussion

Postoperative morbidity and subsequent hazards in the management of a patient with craniopharyngioma have been well documented. However, the increasing numbers of recent reports have indicated that more neurosurgeons are interested in radical resection of the tumor, especially after the technical advances based on the introduction of the surgical microscope and synthetic glucocorticoids. As Matson and Sweet[9,10] have emphasized, the necessity of radical excision of a craniopharyngioma in the initial surgical intervention, especially in childhood cases, can not be ignored. At the same time, Katz[5] noted that a large cystic craniopharyngioma is apt to recur more often than a solid one of childhood. The technical difficulty of resecting recurrent craniopharyngiomas is much greater than in the initial operation and more complex metabolic disorders can not be avoided in the immediate postoperative stage and in the follow-up period. Total resection of the adult craniopharyngioma is followed not infrequently by more difficult to manage metabolic disorders and recurrence is also not insignificant. The object of this paper is not to criticize the extensive resection of tumors which have already caused some deterioration in metabolic functions, but to evaluate radiation therapy in so-called radio-insensitive epithelial tumors. The present study indicated that intracapsular irradiation with 198-Au after simple evacuation of the cyst had sufficient effects in reducing fluid accumulation and preserving endocrine functions. Mass effects on the surrounding structures, especially on the optic chiasm, were greatly improved and about two thirds of the patients showed good visual recovery. The patients who failed to show visual improvement had had the same level of disturbances before treatment, and it was suspected that irradiation had no effect on the visual acuity. Unless the patient had sustained visual disturbances the quality of active daily life was quite satisfactory in all patients in the follow-up study. Case No. 1 had undergone five craniotomies prior to intracapsular irradiation and a single injection of 15 mCi of radioactive gold gave him over 11 years of active life as a policeman until his retirement. Four patients, case Nos. 2, 6, 13 and 15, received treatment while they were of school age and all of them were able to continue school life with no noticeable handicaps. This is unlike the case reported by Frasier[3] where a child with physical retardation due to HGH deficiency showed almost no recovery of satisfactory physical growth after extensive resection of the tumor. Hypophyseal dwarfism was seem to be one of the causal effects in children's psychological or intellectural disturbances. Although the results of crescormon administration to physically retarded children were not totally satisfactory, favorable recovery was observed in children treated with intracapsular irradiation but not in cases of total excision.

Hormonal replacement therapy for various disorders has achieved considerable efficacy in recent years and it can be said that most of the disorders are manageable. Nevertheless, postoperative replacement therapy is less comfortable for the patient and the physician in charge as well, particularly if the patient sustains disorders over a long period. Seven patients, less than half of the cases, required some replacement therapy, although it was not complicated, during the follow-up study. Immediate postoperative morbidity was also much less troublesome and the postoperative polyuria or diabetes insipidus subsided within a shorter period than in cases of extensive surgery.

The surgical procedure for intracapsular irradiation is quite simple and this should be its greatest advantage for the treatment of a patient who may very easily develop complicated responses to stressful maneuvers. Finally, seven patients in our present study were recurrent cases and two of them received multiple craniotomies. It was interesting to find that partial excision of the solid or partly cystic tumor to the permissible extent in the initial operation afforded a better chance for intracapsular irradiation in the second craniotomy since the residual tumor tended to form a large cyst.

The indication of intracapsular irradiation was naturally limited to cystic craniopharyngiomas, and the treatment was not feasible for solid masses which should be taken into account in the second operation. Cases with marked calcification and thick walls were also not good candidates for this treatment. Two patients, case Nos. 5 and 10, eventually underwent resection of the tumor after intracapsular irradiation which showed only a temporary effect in reducing cystic expansion. Case No. 10 had marked capsular calcification and it was evident that the tumor capsule failed to collapse. Histological examination of the resected tumor of these two cases was performed and both indicated significant degenerative changes in the epithelial cell layers and fibrosis due to radiation effects. The tumor capsule was surrounded by gliotic tissue and isolation of the tumor was much easier after intracapsular irradiation. However, it is quite probable that the gliotic envelopment is attained at the cost of cerebral tissue where a number of hypothalamic nuclei are involved. Fortunately, the results of hormonal assays in our study did not offer any evidence indicating aggravation of hormonal dysfunctions in all cases except for case No. 13 which showed moderate elevation of the plasma PRL level after treatment. Selection of appropriate radioactive isotopes and adequate dosimetric estimation are other important problems in this treatment. In this study 198-Au colloid was used and the physical characteristics of this material were found to be very applicable in intracapsular irradiation. The physical half-life is 2.7 days which is favorably short for clinical use. The distance of maximum penetration of the β particles is 3.8 mm and its half-value layer in soft tissue is 0.3 mm, which are ideal lengths of radiation for capsular tissue of a craniopharyngioma. Five percent of the radioactive energy of 198-Au consists of γ rays with 0.41 Mev of energy. Radioactive isotopes with γ emission can be injurious in intracapsular irradiation and if the dosis of 198-Au is not appropriate, it can cause unnecessary radiation damage of the hypothalamus. On the contrary, this disadvantage of 198-Au can also be beneficial when the capsule is thicker than 4 mm or has mural growth. It is most appropriate to apply a radioactive material which has a sufficiently small γ ray energy to cover the shortage of β ray energy, and in this respect 198-Au is the best material.

Leksell[7] has reported a dosimetric method for radiation therapy and there are several other formulae to estimate the total radiation dosis. However, estimation of the suitable dosis is still of a difficult task because the size and shape of the cyst are so irregular in each case. The capsular thickness can be estimated by a cystogram and CT scan or pneumogram, but this is also not completely accurate. In our series, 15 to 30 mCi of 198-Au was applied to cysts with contents of 15 to 50 ml and the total radiation dosis for the capsular wall was calculated by a modification of Leksell's method (Fig. 1). There was no apparent correlation between the estimated dosis and the effectiveness of intracapsular irradiation. Case No. 1, for example, received satisfactory effects with 10,900 rads, whereas an other case, case No. 7, had to receive a second injection after treatment with 104,200 rads. Histological findings or the age of the patients did not support any discrepancy between these two cases.

Further accumulation of cases and careful analysis should offer more useful information for the indication and the limitation of this treatment and, at present, the results of our study appeared to show that it is a better choice of treatment for cystic craniopharyngiomas, especially in recurrent cases.

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