PSEUDOTUMOR CEREBRI

[with special reference to visual loss]

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1. INTRODUCTION

1.1. Definition:

Pseudotumor cerebri is a clinical syndrome characterised by the presence of raised intracranial pressure in an otherwise alert patient. It occurs in the absence of localizing neurologic abnormalities. False localizing signs such as VI nerve paresis are seen in some patients. CSF is normal except for increased pressure and there is no radiological evidence of an expanding mass or ventricular obstruction(1).

The terms Pseudotumor Cerebri (PTC) and Benign Intracranial Hypertension are used interchangeably in the literature. Since it was first described, there has been much argument as to the most suitable name for the disorder. For this reason a brief history of the syndrome is outlined, highlighting some of the interesting and controversial aspects of the syndrome as well as its nomenclature.

1.2. History:

This condition was probably first described by Quincke (2) in 1893. He wrote about a group of chiefly young women who had developed "cerebral symptoms such as headache, vomiting and optic neuritis". A number of these patients recovered completely and no cause could be found for their symptoms. He attributed this phenomenon to the development of a cerebral effusion of serous fluid resulting from altered "vasomotor changes" in the brain which he called angioneurotic in origin. Although some patients probably did have what is today recognised as PTC, Quincke also

suggested that many nervous and so called neurasthenic headaches were due to this cause.

Later in 1913,Warrington (3) described a group of patients who had the clinical manifestations of either acute or chronic raised intracranial pressure.In these patients,the course of the disease (or on occasion the post-mortem evidence) showed the cause not to be due to a cerebral tumour or the "commoner form of meningitis".He attributed this to the occurrence of a serous effusion in the skull which he believed to be inflammatory in origin and a manifestation of some other primary pathologic process.He felt that in many cases a near or distant focus of infection produced toxins which stimulated the vessels of the meninges,brain and ependyma to form a serous effusion.He suggested that the raised intracranial pressure was the cause of the symptoms and required relief independent of its origin.Although Warringtons patients had signs of raised intracranial pressure simulating "the gravest cerebral disease", many subsequently recovered by natural processes or by the aid of procedures such as decompression.Present day scrutiny shows that his patients were largely a heterogenous group which included for example patients with probable tuberculous and other infective meningitides and post traumatic obstructive hydrocephalus.

At almost the same time,Passot had published his thesis in the French literature,the main points of which are discussed in full in the English literature by Sir Charles Symonds (4)(5).He stated that it was important to distinguish those patients in whom the

CSF was abnormal from those in whom the chemical and microscopic examination of the CSF was entirely normal.He believed that any excess of cells or protein in the CSF constituted the preliminary stages of purulent meningitis.He felt that those patients in whom the CSF was normal constituted a distinct clinical group as they presented with neither clinical nor serological evidence of meningeal inflammation.He observed that this condition could be relieved by LP which showed the spinal fluid to be under increased pressure but to be normal on microscopic and chemical examination.He believed that this was due to excess fluid in the subarachnoid space rather than in the ventricles and recognised that secondary optic atrophy and blindness may develop if the condition of increased intracranial pressure was unrelieved.

In 1931,Symonds (5) noted that a not uncommon complication of either acute or chronic otitis media with or without mastoiditis or lateral sinus thrombosis,was a state of raised intracranial pressure which he attributed to an excess amount of CSF which was otherwise normal.He suggested the term "Otitic Hydrocephalus" which implied no active process of inflammation.This term,deprived of the qualification of either "internal" or "external",would,he argued, therefore be inclusive of both fluid in the ventricles and the subarachnoid space.Symonds used the term hydrocephalus in a strict sense to mean an abnormal accumulation of fluid in the head and this was not necessarily accompanied by enlarged ventricles.Although the pathology was obscure,he felt that this was either due to increased secretion from the choroid plexus or a defective absorption through the

arachnoid villi.He recognised that headache and papilloedema were the most consistent findings and also noted the not infrequent occurrence of VI nerve palsies in a number of cases.The temperature and the pulse were normal in this condition and he observed that "mental state may be remarkably clear considering the degree of papilloedema".Earlier papers give much attention to the differential diagnosis (based on clinical parameters and the CSF findings) between this syndrome and other diseases such as obstructive internal hydrocephalus and cerebral abscess (5).

It was not until a report by Davidoff and Dyke (6) in 1936 that PTC was shown to occur in the presence of a normal ventricular system.Case reports in the literature prior to 1936 are open to some doubt as mass lesions had not been excluded on all by air encephalography or carotid angiography.

As different parameters were being defined,by successive authors,so too were different names suggested for the syndrome.As can be seen from the literature many authors have had great difficulty in finding an appropriate name for the syndrome.It has in the past been called Serous Meningitis,Otitic Hydrocephalus, Hypertensive Meningeal Hydrops and Brain Swelling of Unknown Cause.Serous meningitis was refuted as clearly this was not an inflammatory disease.Symonds's suggestion of "otitic hydrocephalus" was also felt to be inappropriate as many patients were shown not to have evidence of middle ear disease and subsequently air studies showed no evidence of hydrocephalus. The term " Benign intracranial Hypertension"(7) dates back to

1955 and is still in use today.The syndrome is considered to be both benign and self-limiting but it may be associated with severe visual loss thereby becoming an extremely urgent condition requiring intervention.The term "benign" refers to the fact that no tumour is found and that the condition does not threaten the patient's life,but it is open to misinterpretation in that it may lead some to believe that the disorder has no serious sequelae.The term "benign" is certainly inappropiate when applied to visual status.For this reason the name "Pseudotumor Cerebri" for the syndrome,is preferred by this author.This study directs particular attention to the visual status in patients with this syndrome.

1.3. Aetiology:

The precise aetiology of this condition remains uncertain and controversy exists regarding the contribution of various factors.

This syndrome has been frequently reported as a result of cerebral venous sinus thrombosis (often following middle ear infection (1)(8) particularly in the earlier reports in the pre-antibiotic era).The literature cites a number of likely mechanisms for the development of PTC complicating a dural sinus thrombosis.The venous sinus thrombosis may increase the intracranial pressure by increasing intracranial CSF outflow resistance and or by direct transmission of elevated intracranial venous pressure to the CSF pathways.In addition,the cerebral swelling associated with the venous occlusion and congestion is

another factor liable to contribute to the development of the syndrome.

With the exception of those patients with venous occlusion,the pathophysiology of intracranial hypertension in the various forms of the disorder is poorly understood. A variety of factors have been implicated in causing this syndrome but the mechanisms are unknown or obscure.

PTC has been noted to be associated with drug ingestion notably tetracycline,naladixic acid,corticosteroid therapy and withdrawal, oral progestational contraceptive agents,and vitamin A.However the use of medications such as tetracyclines or steroids are associated with a very small percentage of the number of cases with PTC in any series.The likelihood of PTC developing during tetracycline or steroid withdrawal is undoubtedly small when the frequent use of these agents is considered.

Obesity as a contributing factor has been noted in as many as 90% of cases in some studies but weight gain just prior to the onset of the disorder is seldom noted. Menstrual irregularities have also been documented in some patients and the syndrome has been observed to occur in pregnancy (9)(10) and in some patients with galactorrhoea.Although the association of PTC with menstrual irregularities,pregnancy and oral contraceptives has been stressed by many authors,these associations occur only in a few patients.Furthermore the incidence of these findings has not been

adjusted for the expected incidence in normal female subjects or otherwise normal,obese female subjects (11).

The syndrome has been recorded in diverse systemic conditions such as iron deficiency anaemia,sarcoidosis,systemic lupus erythematosis,Behcets disease,hypoparathyroidism and Addison's Disease (12)(13)(14)(15)(16)(17).PTC has also been described following various infections such as poliomyelitis,infectious mononucleosis and upper respiratory and urinary tract infections.It is not known whether these illnesses were simply chance associations. Pseudotumor Cerebri has been reported in association with the Guillain Barre syndrome (9)(18).
A small percentage of patients in some series (19)(20) described mild head injury just before the onset of symptoms.These episodes were not severe enough to necessitate hospitalization and were generally reported as mild concussion or even less severe head injuries.Once again it is unclear whether these episodes simply represent chance associations but it is conceivable that some of these patients had traumatic cerebral sinus thrombosis.

In many cases no aetiological agent or disease is identified.

Some authors (11) tend to distinguish between the condition when it occurs as a result of proven dural venous sinus thrombosis and when it occurs without any definite or probable cause. It is likely that the syndrome encompasses a number of different conditions with possible different pathogenic mechanisms.This has lead some workers (21) to reserve the term PTC for the group of

young obese women with the syndrome and no obvious underlying cause. However it is not known whether the pathogenic mechanisms are different in the two groups,nor whether they differ in any way in their presentation or response to treatment.As the term PTC refers to a clinical syndrome and not necessarily a single disease process,it seems pointless to restrict its use to the idiopathic group only.

2. AIMS OF STUDY:

1. To analyse the patients who have been treated at Groote Schuur Hospital over the last seven years for Pseudotumor Cerebri.
2. To document the clinical features of this group of patients.
3. To determine the visual prognosis of this group.
4. To assess the forms of treatment that have been used in this group.
5. To review the literature with regard to:

    a) a comparison of the results of other studies with the present one.

    b) the pathophysiology of the condition.

    c) treatment of the syndrome.

    d) the visual prognosis of the syndrome.

3. DIAGNOSTIC CRITERIA:

There is consensus in the literature concerning the diagnostic criteria for the syndrome. It is largely accepted that criteria for the diagnosis (6)(9)(11)(20)(22)(23) should include the following:

1. The symptoms and clinical signs are due to the presence of raised intracranial pressure alone.
2. Lumbar CSF pressures are elevated above 200mm water.
3. CSF composition is normal in terms of protein, sugar and cell count.
4. Neuroradiological investigations show no evidence of an intracranial mass or ventricular obstruction.

4. METHODS:

1. Retrospective analysis utilizing computer retrieval of all patients admitted to GSH during the last seven years with the disorder.
2. Analysis of Department of Neurology records as well as the entire medical folders of each patient known to have the syndrome.
3. Selection of patients to be included in the study to meet with recognised diagnostic criteria as stated above.

4.1. Parameters:

Analysis of records with regard to:

1. Predisposing or precipitating factors.
2. Clinical perameters including onset, symptoms and neurological signs, including visual deficit at time of diagnosis.
3. Special investigations.
4. Follow-up period and duration.
5. Ultimate visual deficit.

4.2. Patients:

The Groote Schuur Hospital computerised record system was used to identify all patients with Pseudotumor Cerebri admitted between January 1981 and December 1987.
During this seven year period 52 patients were admitted to the hospital where a diagnosis of PTC was made.

Scrutiny of the medical notes showed that in 15 of these patients the diagnosis of PTC was incorrect as the clinical findings and investigations strongly favoured an alternate diagnosis (such as cysticercosis, intracerebral haemorrhage, inflammatory disease, traumatic skull fractures, and cases where the data was inadequate to make a firm diagnosis).

In a further 7 patients the diagnosis was thought to be compatible with PTC but these were excluded from this study because all the diagnostic criteria as outlined above were not fulfilled. These inluded patients in whom the CSF cell count or chemistry are not recorded and those in whom the CSF pressure

readings were inaccurately measured (eg. measured after the CSF was drained or soon after an osmotic diuretic had been given).

A total of 30 patients fulfilled all the diagnostic criteria and were included in this study.

5. RESULTS:

5.1. Sex and Race Distribution:

Total no of male patients: 6

Total no of female patients: 24

Male to female ratio: 1:4

Total no of White patients: 5 (males:1,females: 4)

Total no of Coloured patients: 22 (males:4,females:18)

Total no of Black patients: 3 (males:1,females: 2)

5.2. Hospital Department in which patients were treated:

Patients with PTC were often admitted and treated by different clinical services at Groote Schuur Hospital.The breakdown of where patients in this study were treated is listed below.

GSH Dept:

Neurology Service: 18 patients

Ophthalmology Service: 2 patients

Neurosurgery Service: 2 patients

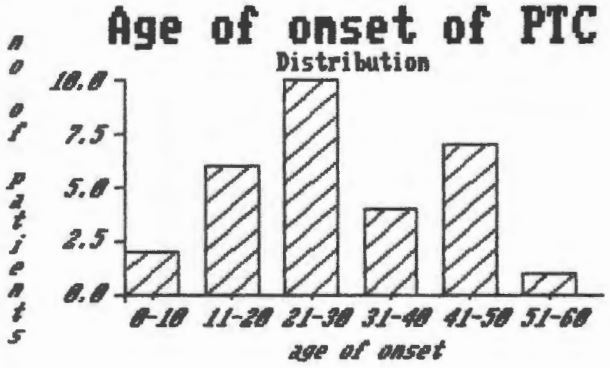
Paediatric Service: 4 patients

Medical Wards: 4 patients

5.3. Age of onset:

Mean age of onset for PTC: 29 years range: 4 to 51 years
Approximately half the patients (14/30patients) developed PTC between the ages of 20 to 40 years.The distribution for age of onset is illustrated graphically below:

Figure no.1



5.4. Associated conditions:

A possible predisposing factor at the time of presentation was noted in 50% (15/30) of the patients in this study.
4 patients had two predisposing factors for the syndrome.
These factors are listed below:

Infections:

4 patients had a history of a febrile "flu-like" illness within two weeks prior to the onset symptoms.
1 patient had an acute left otitis media at the time of presentation.

Minor head trauma:

1 patient gave a history of minor head trauma prior to onset of symptoms.

Drugs:

11 patients were taking one or more drugs known to be associated with PTC at the time they developed symptoms.these include:

tetracyclines:	5 patients
Vitamin A :	3 patients
oral contraceptives:	5 patients
intramuscular contraceptive:	1 patient

(3 patients were taking 2 drugs associated with PTC)

Menstrual irregularities:

2 patients gave histories of menstrual irregularities.

5.5. CLINICAL PRESENTATION:

5.5.1. Symptoms:

Table no.1

A table of presenting symptoms of the 30 patients with PTC is illustrated below:

symptom	number	percent
headache	28	93%
visual obscurations and blurring	18	60%
diplopia	10	33%
vomiting	10	33%
dizziness	3	10%
pain left mastoid area	1	3%
5kg weight gain in 1 month	1	3%

The duration of the headache prior to the diagnosis being made varied from 5 days to 1 year in this group. In 67% of these patients (20/30) the duration of the headache was a month or less. In those patients who complained of headache for a period of 6 months or more (4 patients) it was not possible on retrospective analysis to determine whether this was due to failure of these patients to seek medical attention or whether incorrect medical assessments had previously been made.
The duration of the visual disturbances (which included transient obscurations in one or both eyes or persistant blurring) was less accurately documented in the records but patients with this symptom tended to seek advice within 1 month of onset of this symptom. One patient complained of transient visual obscurations ("black patches before the eyes") for a whole year before coming to hospital.

5.5.2. Clinical signs:

General:

obesity: 16 patients (53%) were recorded as obese

blood pressure: 27 patients were normotensive and 3 patients had mild hypertension (150/100;160/95;and 140/100) on presentation.

papilloedema: 100% of patients had papilloedema

Sixth nerve palsies: 9 patients (30%) had 6th nerve palsies.This was bilateral in 6 patients and unilateral(all on the left) in 3 patients.

other: 1 patient had acute otitis media on admission;

2 patients had mild unilateral lower motor neurone facial weakness which resolved completely on treatment;

1 patient already had optic atrophy at time of first assessment;

1 patient had a cataract;

1 patient had an ejection systolic murmur;

and 1 patient developed painful ulcers on lateral border of her tongue and at venipuncture sites.

5.6. VISUAL FUNCTION (at diagnosis):

Visual function was assessed by testing visual acuity as well as visual fields,with formal perimetry being done in the ophthalmology department.

5.6.1. Visual Acuity:

Best corrected visual acuity was done with the standard Snellen chart.

Normal visual acuity was recorded on 14 patients (47%) at the time of diagnosis (all had acuities of 6/6 bilaterally except for 2 with acuities of 6/7.5).

Visual acuity was not tested at time of diagnosis in 2 patients.

Visual acuity was found to be abnormal in 14 patients (47%) at first assessment.This includes all patients who had visual acuities of 6/9 or worse in one or both eyes.

Visual acuity was impaired in both eyes in 10 patients.

Visual acuity was impaired in one eye only in 4 patients

Visual acuity was found to be 6/18 or worse in either eye in 6 patients (20%).One patient whose vision was reduced by a cataract to counting fingers was not included in this figure.

5.6.2. Visual Fields:

Formal perimetry was done on the Goldmann perimeter,or the Friedmann Field Analyser,or more recently on the automated computerized perimeter.The Friedmann Analyser utilizes a series

of filters which reduce the intensity of the light source thereby increasing the sensitivity of the test.

13 patients (43%) had full visual fields on formal testing at the time of diagnosis of PTC.

5 patients (17%) did not have their visual fields formally tested at time of diagnosis.

12 patients (40%) had impaired visual fields at first assessment (excluding enlarged blind spots).

5 patients had peripheral field constriction (bilateral in 3)

3 patients had impaired visual fields with reduced sensitivity to the filters on the Friedmann Analyser.

2 patients had inferior visual field defects

1 patient had a temporal field defect.

1 patient had bilateral patchy loss of visual fields

Of these 12 patients with impaired fields at first assessment,4 were found to have normal acuities

5.7. VISUAL FUNCTION AT LAST ASSESSMENT:

The visual acuities and fields were analysed at the time of the last clinical assessment in this group of patients to determine the visual outcome.

5.7.1. Final visual acuity:

13 patients (43%) had normal visual acuity at the time of the last assessment.

6 patients (20%) did not have their acuity tested at final assessment.

11 patients (37%) had impaired visual acuity at last follow-up.

Of these 11 patients:

4 patients had final visual acuities in one or both eyes which were worse than their acuities at presentation.

3 patients had improved final acuities compared to presentation.However,1 of these patients developed a rapid bilateral profound deterioration of vision while in the ward,and although final acuity more than a year later was better than at time of diagnosis,the visual fields were still profoundly impaired in this patient.

4 patients had visual acuities which were unchanged at final assessment compared to the initial assessment.

All 11 patients who had impaired visual acuities at last follow-up had impaired acuities at the time of the first assessment.

5.7.2. Final visual fields:

9 patients (30%) had normal visual fields at the time of the last assessment.

10 patients (33%) did not have a final visual field assessment done.

11 patients (37%) had impaired visual fields at the time of last assessment. Compaired to the initial assessment,final visual fields were worse in 4 patients,improved in 1 patient,and unchanged in 4 patients.1 patient developed a new inferonasal defect on the left but had improvement of the previously recorded constricted field on the right.The last patient had reduced sensitivity to the filters on the Friedmann chart at final assessment but as the first chart has been lost,no comparison can be made.

The table on the following page lists the 11 patients with impaired visual fields at last assessment noting the final field defects,duration of follow-up and outcome:

Table no.2: Final Visual Fields

P.no.	Final VF	follow-up	outcome
4.	profound bilat constriction with central depression	15 mths	much worse
6.	bilat field constriction	24 mths	unchanged
8.	patchy field loss on right	2 mths	worse on R.
14.	mild field impairment on the R	8 mths	worse
15.	constricted field on the right	2 mths	unchanged
16.	profound field loss on R	4 mths	unchanged
18.	full fields but reduced sensitivity to filters	9 mths	not known
25.	bilat field constriction	10 mths	much worse
27.	inferonasal field defect on L	12 mths	new defect
29.	mild bilat arcuate constriction	1 week	improved
30.	bilat patchy field loss	2 mths	unchanged

Of the 11 patients with impaired final visual fields,9 also had impaired visual acuity,1 patient (no.27) had normal acuity and 1 patient's final acuity is unknown because her eye clinic record has been lost.

5.7.3. Visual outcome taking both acuity and fields into account:

As visual function was assessed by both visual acuity and visual field testing,it is necessary to look at the combined statistics for both parameters to determine visual outcome.The combined figures are particularly relevant as not all patients had both acuity and fields tested ab initio,and at last follow-up.

A total of 13 patients (43%) had impaired visual function (as determined by reduced visual acuity or reduced visual fields or both) at the time of last assessment.

12 of the 13 patients had reduced visual function (by the same criteria as above) at time of first assessment.

18 patients (60%) had impaired visual function at time of first assessment for PTC.

Of these:

3 patients had normal visual function at final assessment as determined by BOTH visual acuity and fields.

3 patients probably had normal visual function at final assessment but one of the perameters (either acuity or fields) were not assessed at the time.

12 patients were left with a residual visual deficit at last assessment.In 6 of these patients visual function (viz. either fields or acuity or both) was worse at last assessment compared to presentation.

The following three tables reflect the parameters of visual function at diagnosis and at last assessment:

Table no.3:

VISUAL ACUITY AT DIAGNOSIS AND AT LAST ASSESSMENT

	initial assess: no of patients	%	last assess: no of patients	%
Normal	14	(47%)	13	(43%)
not tested	2	(6%)	6	(20%)
Impaired	14	(47%)	11	(37%)

Table no.4:

VISUAL FIELDS AT DIAGNOSIS AND AT LAST ASSESSMENT

	initial assess: no of patients	%	last assess: no of patients	%
Full Fields	13	(43%)	9	(30%)
not tested	5	(17%)	10	(33%)
impaired fields	12	(40%)	11	(37%)

Table no.5:

VISUAL FUNCTION (VFN) AT DIAGNOSIS AND LAST ASSESSMENT
(ie. as determined by visual fields and/or visual acuity)

	initial assess: no of patients	%	last assess: no of patients	%
Normal VFN	11	(37%)	12	(40%)
Impaired VFN	18	(60%)	13	(43%)
no information of VFN available	1	(3%)	5	(17%)

Therefore 13/25 patients (52%) [in whom objective measurements of VFN are available] were left with a residual deficit at last assessment

5.7.4. Fundi at last assessment:

The funduscopic findings were not recorded in 6 patients at the last clinical assessment.

10 patients (33%) had normal fundi at last assessment (with the duration of follow-up ranging from 2 weeks to 4 years with a mean of 15 months).

6 patients (20%) were thought to have improved but still swollen discs (with a follow-up period ranging from 1 week to 18 months with a mean of 6 months).

4 patients still had swollen discs at follow-up (duration ranging from 2 to 33 months).

3 patients had optic atrophy at follow-up (duration ranging from 10 to 24 months).

2 patients had glial tissue around the disc (1 of whom still had swollen discs) at follow-ups of 1 and 3 years respectively.

Of the 15 patients (50%) who had abnormal discs at last assessment,9 had a residual visual deficit (impaired acuity or fields or both).

[Discussion of visual loss and prognosis on page 37]

5.8. CSF Pressure:

Initial pressures were greater than 400 mm of water in 19 of the 30 patients (63%). In the remaining 11 patients the initial pressures were between 200 and 400mm water.

Only a single lumbar puncture was done in 10 of the 30 patients (2 subsequently had LP-shunts inserted). Of note was that 5 of the 10 patients had a residual visual deficit at final assessment.

In the 20 patients who had more than 1 LP, the last recorded LP pressures (which was the second LP reading in 5 of these patients) were:

Normal in 5 patients.

Increased in 15 patients (with pressures of greater than 400 in 8 of the 15)

The following table compares the frequency of various presenting features with visual deficit at diagnosis and at last assessment.

Table no.6:

PRESENTING FEATURES AND VISUAL DEFICITS

	PST	DX	LST	NI
symptoms:				
visual obscurations.....	18	13	11	1
no obscurations.....	12	5	2	4
headache < 1/12.....	18	10	8	3
1/12 to 1yr.....	10	6	3	2
no headache.....	2	2	2	0
age:				
< 20 yrs.....	8	4	1	3
20 to 40 yrs.....	14	9	6	1
> 40 yrs.....	8	5	6	1
sex:				
male.....	6	2	1	3
female.....	24	16	12	2
weight:				
overweight.....	16	7	6	4
normal weight.....	14	11	7	1
predisposing factors:				
precedant illness.....	5	1	1	2
no precedant illness.....	25	17	12	3
drug history.....	11	7	4	3
no drugs.....	19	11	9	2
Initial CSF pressure:				
pressure < 400.....	11	6	5	2
pressure > 400.....	19	12	8	3

PTS = number of patients
DX = number of patients with impaired visual function at time of diagnosis.
LST = number of patients with impaired visual function at time last assessment.
NI = number of patients in which no objective information of visual function is available at last assessment.

5.9. Radiological Investigations:

5.9.1. Skull X-Ray (SXR):

5 patients did not have a SXR taken.

17 patients had normal SXR's.

4 patients had erosion of the dorsum sella on SXR.

1 patient was thought to have an empty sella syndrome on SXR.

2 patients had enlarged pituitary fossae on SXR.

1 patients was noted to have a giant cisterna magna on SXR.

5.9.2. CT Scan:

all 30 patients had CT scans.

22 patients had a normal scan.

5 patients were shown to have small ventricles on the scan.

3 patients had an empty sella on the scan.

5.10. Follow-up Duration of patients with PTC:

The mean follow-up duration of patients in this study was 296 days(ie. approx. 10 months) with a range of 7 days to 4 years.

5 patients had no follow-up at Groote Schuur Hospital (1 patient had recovered completely at time of discharge;3 patients were discharged to hospitals in other centres;and 1 patient was lost to follow-up).

Of the remaining patients:

7 patients were followed-up for a period of between 1 week and 2 months.

6 patients for a period of between 2 and 5 months

2 patients for a period of between 5 and 10 months

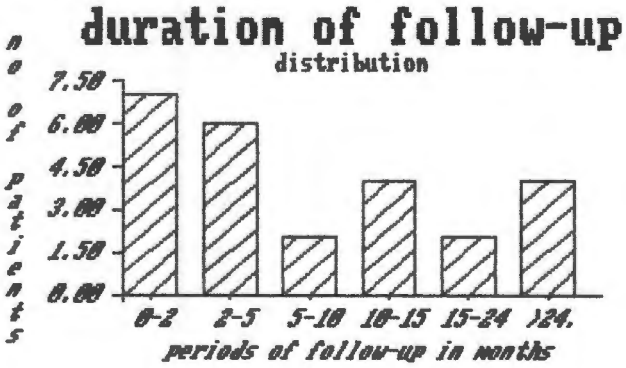
4 patients for a period of between 10 and 15 months

2 patients for a period of between 15 months and 2 years.

4 patients for a period of more than 2 years.

these figures are illustrated graphically below:

Figure no.2



5.11. Relapse of PTC:

4 patients had relapses of symptoms with raised pressure after an initial improvement.This occurred within 6 months of the first episode in all of thse patients.

5.12. TREATMENT:

5.12.1. Repeated Lumbar Puncture:

20 patients had more than one LP:

5 patients had 2 LP's each.

8 patients had 3 LP's each.

6 patients had 4 or more LP's each.

In 1 patient the exact number of LP's is uncertain

5.12.2. Drug therapy:

6 patients did not receive any drug therapy.

11 patients were treated with one drug only (steroids in 3; diuretics in 7;and acetazolamide in 1)

7 patients were treated with 2 drugs.

6 patients received 3 drugs.

5.12.3. Steroids:

A total of 16 patients were treated with steroid drugs.

7 patients were given Dexamethasone (used for 1 month or less in most patients but 1 patient was treated with Dexamethasone for a year)

7 patients were given Prednisone (treated for periods ranging from 5 days to 5 months)

2 patients were given Dexamethasone for a short period and then followed by Prednisone for 2 months.

5.12.4. Carbonic Anhydrase Inhibitors (Acetazolamide):

8 patients were treated with Acetazolamide.

Duration of treatment ranged from 5 days to 5 months.

5.12.5. Other Diuretics:

10 patients received thiazide diuretics,5 patients received furosemide,and 2 patients received chlorthalidone.

Duration of treatment ranged from 1 week to 5 months.

5.12.6. Surgical treatment:

5.12.7. Lumbo-Peritoneal shunt:

These shunts were inserted in 4 patients within 6 months after presenting with PTC. Indications for the procedure were deteriorating visual function and failed medical therapy.

In 3 patients there was no further visual detioration after the shunt was inserted (1 was even shown to have improved thereafter). The fourth patient's shunt had to be removed after 9 months because it had blocked. Visual fields have not been

retested after the removal of the shunt.

5.12.8. Optic Nerve Decompression:

2 patients had had this procedure done for progressive visual failure.This was done in one eye in the one patient,and in the other patient the procedure had to be repeated in the other eye within 3 months of the first decompression.In the first patient there was no further visual loss in the eye after the decompression.The second patient developed bilateral optic atrophy despite decompression to both eyes.

6. DISCUSSION:

6.1. Clinical Aspects:

General:

The age range and preponderance of female patients in this study is similar to that of previous studies.Peak incidence occurs in the third decade (1)(24)(25)(26) with the majority of patients developing the syndrome between 17 and 44 years of age (1)(26).

The mean age of onset for Pseudotumor Cerebri was 29 years which is similar to the mean age of onset in other studies [eg. 27.8 yrs in ref.(26);34 yrs in ref.(27);32 yrs in ref.(22)]

It is striking how similar the bar graphs depicting the distribution of age of onset are in this study of 30 patients compared to that of Johnston's group of 110 patients (20).

Although sporadic cases below the age of 1 year and after the age of 60 years are described,the condition is very uncommon in these age groups.
The figures for patients younger than 12 years in this study are representatively,probably lower than those encountered in the general population.Children are usually referred to the Red Cross Childrens Hospital.

6.2. Associated Conditions:

In half the patients in this study,a specific factor in the patient's history was thought to be significant.In 4 patients

more than one such factor was present.At first glance,the figure is somewhat higher than in many studies.The literature lacks consensus on what constitutes an associated predisposing factor and others which are due to a chance association.
Johnston's figure of 43.6% for "aetiologic factors" includes acute infection,ear infections,head injury and steriods but his chart does not mention factors such as menstrual disturbances,oral contraceptives and drugs such as Vitamin A and tetracyclines (20).

In the present study as in others,values for incidence of menstrual irregularities,pregnancy and oral contraception are not adjusted for expected incidence in normal female subjects or otherwise normal,obese female subjects.Furthermore some patients may have had cerebral sinus thrombosis,a recognised complication of oral contraceptives and pregnancy.Some authors have suggested that any associated female endocrine abnormalities are simply secondary to the increased intracranial pressure.Greer's (28) report of 4 patients in whom amenorrhoea preceded the symptoms of PTC by 3 to 5 months suggests the contrary.
Other studies (1)(22) did not mention or include non specific flue-like illnesses as a possible associated factor.When factors such as menstrual disturbances,acute febrile illnesses,ear infections and drugs such as tetracyclines and Vitamin A are included as possible associated conditions for the development of PTC as they have been in this study,then the figures are similar to other studies (19).

6.3. Symptoms:

Headache was by far the most common and persistent complaint which caused patients to seek medical attention. It was typically generalised, often ill-defined, but not infrequently described as throbbing and worse in the morning. The ophthalmologists are more likely to see patients with visual symptoms who may not have headaches (26). In this study the 2 patients who did not complain of headache presented to the eye clinic. In one series of 107 patients with PTC who were all referred to the neuro- ophthalmology clinics at the National Hospital for Nervous Diseases in Queens Square, 28% did not have headaches as a presenting complaint (23).

In the 28 patients who complained of headache in this study, the symptom had an intensity or persistence which generally caused them to seek medical attention early on. In 2/3 of these patients the duration of this symptom prior to diagnosis was less than or equal to a month.

Both vomiting and dizziness were symptoms which some patients complained of and again the frequency of these complaints are not unlike those of other studies (8)(20).

It is difficult to know what to make of the complaint of a dramatic weight gain just prior to the onset of PTC in one patient. Although obesity is often quoted in many studies as a common finding in these patients, this is usually a long standing problem.

6.4. Visual symptoms:

Diplopia was encountered in 33% of patients in this study and this frequency is similar to other studies (8)(20).The diplopia is usually caused by a VI nerve palsy which generally resolves and is ascribed to a non-specific effect of raised intracranial pressure.

Disturbances of visual acuity such as transient visual obscurations or fading of vision lasting a few seconds,or visual blurring lasting minutes to hours or even persisting was recorded in 60% of patients.The frequency of subjective visual disturbances other than diplopia varies from 30% to 72% depending on the study (1)(19)(20)(22)(26).

6.5. CLINICAL SIGNS:

6.5.1. Obesity:

In virtually all series a high percentage of patients were obese ranging from 44% (20) to 90% (1).Approximately half the patients in the present study were thought to be clinically obese.Ahlskog (11) has briefly reviewed some of the controversial speculations which have arisen suggesting that obese female patients may be more prone to PTC because of elevated estrone levels,a hormone produced almost exclusively by adipocytes.Increased levels in obese females may explain menstrual irregularities not infrequently found in these patients.

6.5.2. Papilloedema:

The most prominant physical sign in all series is the presence of bilateral papilloedema which was present in all 30 patients.Unilateral papilloedema was not seen in this group but has occasionally been described (29)(30).

The appearance of the papilloedema cannot reliably differentiate between PTC and other causes of increased intracranial pressure.While the disc in the peripapillary region may show haemorrhage and exudate,haemorrhage at the periphery of the retina is very rarely seen (31).If the disc has become considerably atrophic,swelling of the disc with recurrent bouts of increased intracranial pressure may not occur (31).In patients in whom papilloedema subsides,the optic discs may appear normal.Some patients have pale "muddied" discs with poorly defined margins typical of secondary optic atrophy or perivascular gliotic sheathing or both,plus a circumpapillary pigment margin.Glistening pseudodrusen,optociliary colateral vessels, and atrophic elevation of the disc may also be seen(31).

6.5.3. Sixth nerve palsies:

30% of patients in this series had VIth nerve palsies and these resolved with treatment of the raised intracranial pressure.This finding is similar to those described in other studies (1)(20) and is thought to be a false localizing sign.

Two patients had lower motor neurone Facial nerve weakness which also disappeared on treatment.This has occasionally been reported

in patients with in PTC (7)(32)(33) and is also thought to be a false localizing sign.

7. VISUAL LOSS IN PTC:

7.1. Mechanism of visual loss in PTC:

Visual loss in PTC results from the effects of chronic elevation of intracranial pressure on optic nerves.A number of factors operative at or near the optic disc are considered important.In the majority of cases the evidence favours chronic ischaemia of the optic disc secondary to optic disc oedema as the major factor (23)(34).The normal prelaminar region of the optic nerve head lies in a restricted space surrounded by an unyielding Bruch's membrane and contains nerve fibre bundles,intervening glial septa and fine vessels lying in the septa.Experimental models have been developed to investigate the pathogenesis of optic disc oedema in raised intracranial pressure.

Raised intracranial pressure is transmitted by CSF to the sheath of the optic nerve.The rise of CSF pressure within the sheath produces a rise of tissue pressure in the optic nerve with resultant stasis of both rapid and slow components of axoplasmic flow in the optic nerve head anterior to the lamina cribrosa (35).This accumulation of axoplasm causes swelling of the nerve fibres in the optic nerve head perhaps because the lamina cribrosa acts as a mechanical barrier to more distal passage of neurofilamentous masses (35)(36)(37).The optic disc oedema then causes secondary vascular changes in the optic disc and peripapillary retinal vessels.The swelling of axons in a

restricted prelaminar region compresses the intervening tissue and the fine venules and capillaries are likely to be the first victims.Venous stasis and slow filling of the prelaminar capillaries occurs (34)(35).Compression of the fine vessels on the surface of the discs by swollen axons produces dilatation,formation of microaneurysms and haemorrhage on the disc as well as in the neighbouring retina.Similarly the central retinal vein is also compressed producing retinal venous engorgement.These vascular changes in the optic disc may produce breakdown of the normal optic nerve-blood barrier and lead to an accumulation of extracellular fluid which is reported on electron microscopy in well-developed optic disc oedema (38). Compression of the intervening tissue may be further aggravated by the extracellular fluid accumulation.Angiographic studies in such eyes have shown circulatory stasis in the perilaminar region of the optic nerve (23)(34).Optic nerves are not compressed in the optic canal as the oedema involves only the optic nerve head in front of the lamina cribrosa sclera with no oedema of the rest of the optic nerve.Compensatory changes such as the formation of optocillary shunt vessels and peripapillary subretinal neovascularization and decompensatory vascular change may contribute to the visual loss.Subretinal neovascularization,with subsequent serous detatchment and haemorrhage does not damage nerve fibres directly but disturbs pigment epithelium and receptors.If haemorrhage involves the fovea,visual acuity is usually reduced (23).

The development of optic atrophy in these patients is also due to

ischaemia of the optic disc and fluorescein angiography has confirmed reduced vascularity in the atrophic discs (34). Sudden visual loss in PTC has been found to be due to ischaemic optic neuropathy and subretinal haemorrhage from neovasclar membranes (39)(40)(41)(42)(43).

7.2. Visual deficit and prognosis in present study:

47% of patients (14/30) in this study had impaired visual acuity at time of diagnosis and in approximately half of these the impairment was severe (viz: 6/18 or worse).

40% of patients had impaired visual fields at diagnosis.This figure would probably have been higher if all patients had formal perimetry (17% of patients did not have their fields formally tested).The defects of visual fields in the above patients have already been outlined and are similar to those noted in the literature.Characteristic field patterns are related to involvement of the optic disc.Enlarged blind spots,inferior nasal defects,arcuate defects,concentric constrictions and centrocaecal and paracentral scotoma may all be seen.The susceptibility of these fields in this disorder affecting the optic disc relate to regional structural differences yielding certain fibres more vulnerable to mechanical and ischaemic damage (26).

The enlarged blind spot is often found in papilloedema and has in the past been attributed to either compression and displacement of the retinal peripapillary percipient elements by the swollen optic nerve fibres or the Stiles- Crawford effect (the latter

phenomenon proposes that wrinkles and folds in the peripapillary retina cause light to fall obliquely on photoreceptors,thus making the light a less effective stimulus).These long held beliefs fail to explain recent observations in which the blind spots in patients with papilloedema were reduced to near normal size by useing progressively stronger plus lenses.This suggests that the enlarged blind spots associated with papilloedema are predominantly a refractive scotoma due to local peripapillary hyperopia (44).This local hyperopia is induced by elevation of retinal percipient elements surrounding the swollen disc.
In view of these observations that increased blind spot represents a refractive error in these patients,the three patients noted to have increased blind spots without other field defects have been included in the group with normal fields.

Visual fields,if correctly done,are almost certainly the more sensitive means of detecting visual loss in these patients. Visual acuity reflects largely macular function.Four patients with normal visual acuity had impaired fields when first tested.

A total of 18 patients (60%) had impaired visual function as determined by either decreased visual acuity or fields or both at the time of diagnosis.

Visual prognosis:

As previously indicated,43% of patients (13/30 patients) had decreased visual function at the time of last assessment.It is interesting to note that the majority (12 out of 13 patients) had

impaired visual function at time of diagnosis,and only 1 patient developed impairment while under observation.More noteworthy,was that in 6 of the 12 patients with a residual deficit,visual function had deteriorated from the time of first assessment.A number of statistical factors must be taken into account when considering the figure of 43% as quoted above.This figure does not take into account 4 patients who were not followed up and another patient who had neither visual acuity or fields tested at follow-up visits,so that for these 5 patients no objective information is available as to visual function at follow-up.Therefore,13 patients out of a total of 25 patients (in whom objective measurements of visual function are available) ie. 52% of patients had a residual visual deficit at last assessment.In these 13 patients the mean period of follow-up was 12 months with a range of 1 week to 3 years (more than 60% of these patients were followed-up for 8 months or more). Furthermore,this statistic reflecting the number of patients with permanent visual deficit due to PTC,is likely to change in the future as the period of follow-up continues.Clearly in some of these patients the disease was probably still active as at the time of last clinical assessment,5 of the 13 patients with a residual deficit were still noted to have swollen discs at ophthalmology clinic.

Certain other factors also merit discussion when considering the frequency of visual impairment in patients with PTC.The method of testing visual function as well as the sensitivety of the test will determine the accuracy of the overall assessment of visual

function.As previously mentioned not every patient in this study had both acuity and fields tested at each visit.Visual field testing is time consuming and requires good patient co-operation, and a skilled technician to do the test properly.A rushed technician in a busy outpatient department who does eg. Friedman perimetry without using all the filters or checking each point on the screen will produce imperfect field results.Sensitivety of field testing is discussed later in the text.
The extent of visual deficit has been described previously,but I have not attempted to determine the resulting disability.The disability of visual impairment is largely dependent on the visual needs of a particular patient (eg. a pilot who develops a slight impairment of acuity eg. 6/9 in one eye or a small scotoma is likely to be aware of the defect and seek attention early,whereas an elderly retired patient with low visual requirement who develops a profound loss of acuity or field may often not even be aware of the loss).

It is clear from the present study that of those patients who were followed-up at GSH,52% had a residual impairment of visual function after a mean duration of follow-up of 1 year.This figure is higher than the frequency of visual loss quoted in a few reports in the literature which emphasize the benign nature of the syndrome with regard to visual prognosis.The basis for this optimism is insecure.

7.3. Frequency of visual loss in PTC in other studies:

Some authors (9)(44) have emphasised the benign nature of the syndrome with regard to visual prognosis.This has led some to believe that the term "Benign Intracranial Hypertension" refers to a benign visual prognosis.

Rabinowicz et al (45) described 8 patients with chronic papilloedema and elevated CSF pressures lasting up to six years in whom visual acuity was normal in all (but 2 who developed optic disc pallor without apparent functional loss and 3 who had persistant nasal defects).As the visual acuity was normal and no decompressive procedure was done,the authors stressed the benign visual prognosis in this small group of patients.They felt that fluctuations known to occur in PTC could explain why in these patients the optic nerve withstands pressure so well.They did however acknowledge other case reports in the literature of PTC in which early development of optic atrophy and ultimate serious visual loss is described.They suggested that there may be a threshold below which intracranial pressure must fall for adequate periods if the optic nerve is to be spared the consequences of prolonged pressure.Although the prognosis regarding visual deficits is reported to be good in the Lysak study (25),the selection criteria were arbitrary and CSF pressures were not recorded in most of their patients.Guidetti (24) also speaks of the "favourable outcome irrespective of treatment" in 80 of his patients with PTC whom he was able to follow-up for periods ranging from 3 months to ten years.He then briefly mentions 12 patients (15%) who had residual visual

defects which were either unchanged or worse than when first seen and fails to expand on this group. In the Weisberg series (1) only 3% of patients had permanent visual sequelae but then field examination was not routinely done at follow-up.

There is ample evidence that visual deficits in PTC are not as infrequent as these reports suggest.

In Dandy's series (46) of 22 cases, 11 had evidence of impaired visual function at presentation (decreased visual acuity, increased blind spot, scotomata or blindness). The majority of these patients were treated by subtemporal decompression. Two patients were left with permanent visual loss despite the decompression. He does acknowledge that his cases may reflect the most severe grades as he was aware of other cases who got better spontaneously without treatment.

Foley (7) reported permanent visual impairment in 12 of his 47 patients (25%) and this was severe in 3.

In Boddie's (22) study, patients with PTC were followed up for six months to twelve and a half years with a mean follow up duration of six years. Twenty three percent (8/34 patients) had visual changes resulting from PTC, and in 12% (4/34 patients) the visual deficits were of a marked degree (eg: secondary optic atrophy and progressive field restriction). Subsequently Bulens (47) also found that 24% of his patients (8/33) had visual impairment at follow-up and Wall, in his initial retrospective study (48), quotes a similar figure of 27% of patients with PTC (12/45) having visual deficits (in 7 of the 12 patients these deficits were

permanent and in the remaining 5 the period of follow-up was inadequate to determine final outcome).In Sorensen's group of patients,25% had abnormal fields when first tested (49).

Orcutt (23) specifically looked at visual function in 107 patients with PTC,followed for at least 5 years,and found detectable visual field or visual acuity loss in 49%.In addition 31% of the total number of patients continued to deteriorate during the period of observation and 6% had very severe visual loss.
These figures are similar to those of the present study.

It is self evident that the incidence of visual loss in many series will depend on the method and sensitivety of the test used for testing visual function and the frequency which the test is done.In many of the retrospective studies,formal visual field examination has not been reported in detailed fashion.The visual field strategy used is very often not specified in these studies.
Wall (50) subsequently studied 20 consecutive patients with PTC with the period of follow-up from the onset of the study ranging from 4 months to 2 years.Fourteen of his patients were still in the active stages of their disease and the remaining 6 had a definate prior diagnosis of PTC but their symptoms and papilloedema had resolved.They performed visual field examinations serially on these patients using a modified Armaly-Drance visual strategy with a Goldman perimiter.This technique carefully tests the central 30 degrees and the nasal

horizontal meridian.In addition,he also did careful automated threshold perimetry (computerized) in the usual fashion with an automated perimeter.This was set to carefully test the central 30 degrees at 6 degree intervals offset 3 degrees from the horizontal meridian.He clearly demonstrated that the frequency of the visual defect detection was highly dependant on the visual field strategy used.He showed that 77.5% of eyes had visual loss detected by automated perimetry and 75% of eyes had evidence of visual field loss by manual perimetry.These figures were 50% greater than highest rates of detection in prior series.Routine screening strategies show visual loss in about 1 in 4 eyes tested but with the more sensitive strategies used in this particular study 3 in 4 eyes had some visual loss.The morphology and frequency of most defects in their patients was similar to those in the previous series.Loss on the nasal side of the visual field especially the inferonasal loss and constriction of the field were the most common defects.They also found a high incidence of scotomas of the paracentral,central and cecocentral variety.

7.4. More sensitive strategies to determine visual loss:

As therapy for PTC is determined by the degree and progression of visual loss these authors (50) recommend that a specific more sensitive strategy (such as manual perimetry with the Armaly-Drance type algorithm rather than routine screening perimetry) should be used for the determination of visual loss.These techniques would offer the opportunity for corrective therapeutic action in the face of demonstrable deteriorating

visual fields long before the patient became aware of already extensive visual fall-out.

Contrast sensitivity testing is a relatively new method of evaluating afferent visual function.It can be performed quickly and inexpensively using Arden plates by measuring a subjects ability to detect differences in shades of grey of a bar grating pattern.Loss of contrast sensitivity with preservation of normal Snellen acuity has been found in diseases affecting the sensory visual system.This test has been shown to be significantly more sensitive than Snellen acuity in identifying visual loss in patients with PTC.It was also superior in serially following patients as there was a significant improvement in contrast scores and papilloedema grade but no significant change in Snellen acuity when the patients were analysed as a group.The advantage of this test is that it can be done quickly at the bedside(51).

7.5. Visual Prognosis in Childhood:

Contrary to statements in the literature,youth does not seem to confirm any protection for visual loss in PTC.Lessell et al (52) described 5 children with PTC who suffered permanent visual loss of acuity or fields in association with the disorder.All 5 had impairment at the time of diagnosis and 2 went on to develop further visual failure while under observation.Baker (53) reported similar findings in 6 out of 36 children with PTC who were left with permanent significant impairment.He noted that more patients with dural sinus thrombosis had serious visual loss than did those with other associated disease or idiopathic PTC.

Children and adolescents should be kept under the same close ophthalmic surveillance as has been advocated for adults.

7.6. Factors predicting visual outcome:

It is clear that none of the clinical features represented in detail in table no.6 on page 26 could be used to predict the presence or absence of visual impairment.The presence and duration of headache could not be used to determine whether patients would have a deficit or not.Of the patients presenting with headache there appeared to be a better outcome among those with the symptom for more than one month.However the lack of objective information of visual function at last assessment in 5 patients precludes confirmation of this.

Factors such as age of patient,sex,obesity,precedent febrile illness or drug therapy did not predict whether or not patients would have visual impairment at diagnosis.

The severity of the condition as judged by opening lumbar puncture did not predict the presence or absence of visual impairment at the time of lumbar puncture.Indeed of the 19 patients with initial pressures greater than 400mm water at least 6 had normal vision at that time.

The symptom of transient visual obscurations or blurring of vision did not allow prediction of visual loss in this syndrome at time of diagnosis,since patients without these symptoms were also found to have had visual impairment at time of diagnosis. However patients with these symptoms were more likely to have visual impairment compared with those without these symptoms.(72% versus 41% at time of diagnosis).

Factors predicting visual loss in other studies:

Boddie (22) analysed his group of patients to see if there were any features of prognostic significance.The age and sex of the patients,duration of preceding visual disturbance,headaches,CSF pressure,and treatment employed (except for 3 of the 4 patients with severe visual loss who had subtemporal decompression presumably reflecting the severity of the visual impairment at presentation) did not prove to be of prognostic value.One feature of note was that 3 of the 4 patients with severe visual loss at follow-up had their visual symptoms and signs at the time of initial presentation.

In another study Orcutt also attempted to see whether specific ophthalmologic features allow prediction of which eyes may lose visual function.Chronicity of papilloedema did not correlate with visual loss but those who had atrophic papilloedema had lost visual field and continued to do so under observation.Not surprisingly,the degree of oedema,which was graded by fundus stereophotography,was found to correlate with visual loss (60% of the patients with high grade papilloedema developed visual loss as compared with 10% with low grade papilloedema).Furthermore, subretinal haemorrhage near the disc was associated with a statistically significant increase in visual loss and it was felt that this disturbance of vascular supply contributed further to the ischaemia of the optic disc (23).Although the symptom of transient visual obscurations do not allow prediction of visual loss in this syndrome,it is interesting to note that in this series the percentage of patients who complained of transient

visual obscurations and suffered severe visual loss was significantly higher than that of the overall group (89% compared to 50%) suggesting that patients who do not complain of visual obscurations are less likely to get severe loss of visual function (23).

7.7. Rate of visual loss in PTC:

Major reviews describing visual complications of PTC often omitted detail on the time course of visual loss (7)(19)(20)(22)(24).The pace of visual loss in PTC is often difficult to determine since visual fields may dramatically constrict without subjective visual disturbance until late.Also the history of symptoms is not useful in determining the tempo of visual loss (26).

Visual loss in PTC is usually gradual or stuttering but may be insidious and occur any time during the course of the disease,even months or years after the diagnosis has been made (26)(39)(47).

Acute visual loss,although not often reported,undoubtedly occurs in PTC.The following case report from the present study illustrates the precipitous manner in which visual loss may occur in a patient with this syndrome.Furthermore,this particular patient developed the precipitous visual loss while she was in the ward under observation.

7.7.1. Case Report:

A 24 year old female was admitted to Groote Schuur Hospital with a complaint of a months' history of increasingly severe headache,worse in the morning and accompanied by nausea and vomiting.In the week prior to presentation,she had noticed transient episodes of blurred vision,occurring intermittently throughout the day.She had no history of drug ingestion,recent gain in mass or menstrual abnormality and had never received a hormonal contraceptive.Examination revealed an obese young woman who had bilateral papilloedema.Visual fields and acuity were normal on bedside testing as was the remainder of the general examination.Radiographs of the skull demonstrated an enlarged pituitary fossa and subsequent CT brain scan was normal apart from small ventricles and an empty sella.A presumptive diagnosis of Pseudotumor Cerebri was confirmed by lumbar puncture,the pressure being greater than 500mm water and cerebrospinal fluid normal in composition.The patient's headache was immediately relieved by the lumbar puncture and thereafter treatment with acetazolamide was commensed.The following day the headache returned and over the ensuing week her visual status deteriorated,despite doses of furosemide and dexamethasone,accompanied by repeated tapping of CSF.One week after admission her visual acuity had deteriorated to detection of hand movements only in the right eye and 6/60 in the left eye,with markedly constricted visual fields and bilateral 6th nerve palsies.From the third day of therapy,headache and symptoms of raised pressure disappeared

whereas her visual function progressively worsened.Surgical intervention was required and a lumbo-peritoneal shunt was inserted.Thereafter the patient's signs improved and 2 weeks after surgery,visual acuity was 6/12 in the right eye and 6/18 in the left eye and the 6th nerve palsies had resolved,but residual fields remained severely constricted.One year later,her visual acuity was 6/9 and 6/12 but her fields still showed constriction with central depression.

Other isolated reports in the literature have described acute visual loss in Pseudotumor Cerebri.

One patient in the Weisberg series (1) was documented as having acute loss of vision occurring over a period of 1 week.

Acute ischaemic optic neuropathy and subretinal haemorrhage from neovascular membranes have caused sudden visual deficits (42)(43).Green et al described a patient with PTC who developed acute visual loss in one eye and was found to have acute infarction of the distal portion of the optic nerve.Troost's patient also developed sudden visual loss secondary to retinal detatchment caused by haemorrhage from a peripapillary neovascular membrane.Subretinal neovascular membranes may be stable for weeks to months and then involute or undergo rapid enlargement.These lesions must undergo photocoagulation before it becomes unsafe to do so (ie. when the lesion spreads beneath the capillary free zone) (41).

In one series,patients had variable rates of vision loss with minimal symptoms.The loss was insidious and was not detected clinically until it had become profound (26).In this series the

diagnostic criteria of the syndrome for inclusion of patients into the study were carefully met and the 57 patients were followed-up for between 5 to 41 years.Of these 57 patients,14 (25%) patients had blinding visual loss or severe visual impairment in one or both eyes and in 7 this occurred months to years after the initial symptoms.

8. DURATION OF ILLNESS AND RECURRENCE:

A number of factors make it difficult to draw firm conclusions about the duration of the syndrome. The onset and end point are not easily definable. The duration of symptoms is not a reliable indicator of the presence of raised intracranial pressure (26).Patients without headache may develop visual deficit without being aware of it and symptoms may disappear but the disease can still be active.Often patients are discharged before papilloedema subsides and even then papilloedema is of limited use in determining the duration of PTC (26).The resolution of papiloedema may lag behind the resolution of raised pressure and the development of optic atrophy may obscure the presence of persistently elevated intracranial pressure.Further,when chronic gliotic changes develop,it is impossible to use disc protrusion to monitor intracranial pressure (49).CSF pressure is the only true objective measurement of the persistence of the syndrome.It is frequently not done at follow-up especially if the patient is asymptomatic and has no visual deficit.

At ophthalmology clinic where patients were followed-up after discharge,attention was directed to detection and prevention of visual deficit.Persistent symptoms such as headache were often not recorded in the notes.Certainly lumbar puncture was not done routinely at last assessment.Also the period of follow-up was too short to make meaningful conclusions about the duration of the syndrome in some of the patients in this study.
These reservations must be borne in mind in observing that 10

patients had normal discs at last assessment and 14 had persistent abnormalities with follow-up periods ranging from 1 week to 4 years (see detail section 5.7.4. Page 24).

It is interesting to note that in Sorensen's group of 24 patients with PTC who were followed-up prospectively for an average of 4 years,the optic disc findings at last assessment were similar to this study.In 50% of his patients papilloedema resolved completely and the remaining 50% had abnormal discs (gliosis of discs,papilloedema,optic atrophy) at last assessment (49).

No single study has documented the course of this syndrome by consistently documenting normal intracranial pressures when all symptoms have subsided and clinical signs remained static.Most of the clinical studies have been directed to the visual prognosis rather than documenting the precise endpoint of the syndrome.All these factors previously mentioned are compounded by the fact that assessment of the duration of the syndrome should be related to the different types of treatment used.This becomes difficult as the indications for different therapeutic options varies considerably,not only from one series to another,but even from patient to patient within any given series.Certain therapeutic measures such as lumboperitoneal shunts in severe cases make it difficult to judge the natural history of these cases.Despite these complex considerations the literature does give guidelines and impressions about the course of the disease.

Foley (7) looked at the onset of first symptoms of raised intracranial pressure to the time when papilloedema symptoms

vanished. In 33% of his patients (18/55) the symptoms and signs of raised pressure lasted less than 3 months, in a further 49% of patients (27/55) the symptoms and signs lasted between 3 months and 1 year and in the remaining 18% they lasted more than 1 year.

Boddie (22) also gives an approximate assessment of duration illness in 24 patients in which adequate information about the duration of symptoms and signs after diagnosis was available. He divided his patients into subgroups depending on treatment received. Mean duration of follow-up was 6 years (with a range of 16 months to 12.5 years). He found that symptoms and signs of raised pressure resolved in:

7 patients (29%) with no treatment -within 1 to 8 months (mean 3 months)

7 patients (29%) with treatment with steroids only -within 4 to 24 months (mean 8.5),

4 patients (17%) treated with steroids and repeated lumbar puncture- within 3 to 14 months (mean 7.5 months),

3 patients (13%) with repeated lumbar puncture only -within 2 to 10 months (mean 6 months),

3 patients (13%) treated with subtemporal decompression and medical treatment -within 2 to 12 months (mean 5 months).

Johnston and Paterson's study (20) did not correlate duration of disease with treatment. They found that in the majority of

patients in their series symptoms did not persist long after starting treatment eg in 83 out of 99 patients,who presented with headache,the headache disappeared within 3 months of starting treatment and in only 9 out of 99 did headache persist for longer than a year.However papilloedema persisted for longer (in 44% of their patients papilloedema resolved within 3 months,in 41% of patients papilloedema resolved within 4 months to 1 year and in 15% of their patients papilloedema lasted longer than a year).In a prospective trial,Sorensen et al (49) observed that 70% of patients had no symptoms of intracranial hypertension 3 months after start of treatment whereas only 20% had normal disc appearance.

In Weisberg's series 27 of the 120 patients had a benign brief illness lasting less than 3 months without treatment and with a normal CSF pressure on the second lumbar puncture.Noteworthy was that in the 120 patients, 50% had been follow-up for at least 2 to 10 years and none developed a brain tumour (1).
In another series (47) the duration of papilloedema from diagnosis varied between 2 weeks and 2 years.However no lumbar puncture was done at last assessment.
Although PTC is said to be a self limited condition (1)(22)(25)(45) there is evidence to suggest that at least in some patients it may be a chronic process (26)(49)(54).In the severe cases there is no doubt that the disorder may persist for several years.Repka et al (55) sucessfully treated 2 patients with idiopathic PTC with lumbo-peritoneal shunts.When these shunts

were removed electively several years later both patients experienced a rapid increase in intracranial pressure and in 1 this resulted in bilateral visual loss.In another report 6 patients with PTC (54) had headaches and papilloedema which resolved but the serial CSF pressures remained elevated (300 to 500mm of water) for 3 to 14 years (4 of the 6 had serious visual defects which persisted despite resolution of papilloedema and headache).The author suggests that these patients may represent a subgroup in whom CSF pressures are reset at elevated and constant levels reflecting chronic disease.The clinical presentation of headache and papilloedema may represent an acute period of worsening in what is otherwise a chronic illness (54).

Recurrence:

13% of patients in this study (4/30) had relapse of symptoms with raised pressure after an initial improvement,occurring within 6 months of the first episode in these patients.

In Weisberg's series,12 of the 120 patients had recurrence and this occurred within 12 months in each patient.

In the Johnston series 11 of the 110 patients developed a recurrence of the original symptoms and signs after intervals ranging from 4 months to 14 years,and 3 of these 11 developed a second recurrence giving a total of 14 recurrences.Bulens series had a recurrence rate of 6% also occurring from months to years after the original episode.

8.1. Conclusions:

The above evidence suggests that approximately 30 to 40% of patients who present with PTC will have a short limited illness

lasting approximately 3 months or less from the time of diagnosis.These studies suggest that clinical symptoms and signs of raised pressure resolve within 1 year in approximately 80% of patients (1)(7)(20)(22)(47).In the remainder the course is likely to be more protracted lasting many months to years after diagnosis regardless of treatment.Ten percent recurrence is the average recurrence in most series and this may occur even years after the first spell (19)(22)(26).At the time of presentation no single factor has been isolated which reliably predicts which patients have a short illness and which will have a more protracted course.Besides the visual sequelae,patients with the syndrome have a good prognosis as long term follow-up has shown that they do not develop brain tumour (1)(56).

9. INVESTIGATIONS:

9.1. Lumbar puncture:

Lumbar puncture should be done on every patient to confirm the diagnosis.It should be deferred until CT scan has ruled out the presence of an intracranial mass.Rush (19) has previously stated that the availability of CT scan has precluded routine lumbar puncture in some patients with PTC.Most workers however,would take issue with this idea as CT scan will fail to identify patients with pleocytosis and may lead to the inclusion of patients with inflammatory disease.Causes of disc oedema such as sarcoidosis or syphilitic meningitis and meningeal carcinomatosis may mimic PTC (13)(57)(58).

9.2. Radiology:

9.2.1. Skull Xray:

Plain films of the skull are usually normal but may show signs of prolonged increased intracranial pressure.Symmetrical enlargement of the sella is not uncommonly reported.

9.2.2. CT scan:

The diagnosis of PTC must be ascertained by the exclusion of other causes of papilloedema and increased intracranial pressure without localising signs.In the search for such clinically silent intracranial lesions such as frontal mass or bilateral subdural haematoma the CT scan has almost completely supplanted angiography and air encephalography,avoiding the complications associated with these invasive procedures (31).The CT scan with contrast enhancement shows no abnormality in PTC,with the ventricular system either normal or reduced in size.
In the present study 17% of patients (5/30) had small ventricles on CT,a figure similar to that in Weisberg's study (59).This author observed that the visual impairment in PTC was not related to CT abnormalities as visual loss occurred in patients with both normal and abnormal CT.Also interesting in the study was the fact that all patients with CT evidence of small ventricles had symptoms for less than 14 days with CSF pressures of 430mm water or more.These pressure values were higher than those with patients with normal size ventricles.This pattern of non visualization of ventricles and basal cisterns correlated with the high CSF pressures (59).In the present study these findings

were not corroborated as the presence of small ventricles was not found to be associated with statistically significant higher CSF pressures compared to those patients with normal ventricular size on CT.

As some patients with non localised increased intracranial pressure may have a dural sinus occlusion,it is important to look for CT signs of the condition.These include small ventricles and a delta sign,which represents a filling defect caused by a clot in the saggital sinus.

9.2.3. The Empty Sella Syndrome:

Three patients (10%) had an empty sella on CT in this study.

The empty sella syndrome is sometimes seen and is known to be associated with PTC.Chronic elevation of intracranial pressure such as occurs in pseudotumor cerebri,if the diaphragma sellae were deficient,produces herniation of the subarachnoid cistern into the sella turcica,with resultant flattening of the pituitary gland and enlargement of the sella (60).The contents of the sella have been compressed greatly usually without loss of endocrine function function owing to probably a congenital defect in the diaphragma sellae.Infrequently,endocrine abnormalities have been found in the presence of the empty sella syndrome (61).It has been suggested that herniation of the optic nerves and chiasm into the empty sella may produce visual loss in these patients.However Corbett found that an empty sella conferred no statistically significant risk for severe visual loss when compared with a normal sella (26).The incidence of empty sella syndrome was 24% (14/57 patients) in his series.

9.2.4. Angiography:

The advent of CT scan has largely repaced angiography and air encephalography as the investigation of choice to exclude a mass in suspected cases of PTC.Since serial angiography is no longer routinely done,more dural sinus thromboses occurring in association with PTC are probably going undetected.It has been shown that patients with underlying dural sinus thrombosis may have symptoms,signs and a clinical course which is indistinguishable from other causes of PTC (8)(62).

In the present study,digital subtraction venous angiography was only done on 2 patients.On one patient the study was normal and on the second patient,a superior sagital sinus thrombosis (with no evidence of lateral sinus thrombosis) was demonstrated.Digital subtraction venous angiography is an ideal test to exclude dural sinus thrombosis.The contrast is administered intravenously and it does not carry the same morbidity and risk as arterial angiography.

10. UNDERLYING DISORDERS:

One patient in this study subsequently developed painful ulcers on the lateral border of the tongue and at venipuncture sights.Angiography revealed superior sagital sinus thrombosis and it was felt she had Behcets disease.[There are similar isolated reports in the literature of Behcet's disease presenting as PTC (63)].Another patient developed anterior uveitis one year after

the first episode of PTC.Serological screening for collagen vascular diseases were all negative and there was no evidence of sarcoid or Behcet's disease.This may become manifest in the future.

In the remaining 28 patients,no underlying systemic disease was found to be associated with the PTC syndrome.

In order to place the various approaches to treatment in perspective,I have elected to briefly review some of the relevant literature concerning the pathogenesis of the syndrome.

11. PATHOGENESIS:

Under normal conditions,intracranial volume includes brain and interstitial fluid (about 80%),CSF (10%) and blood (10%).It is recognised that an increase in the volume of one compartment must be accompanied by an approximately equal decrease in the volume of the other compartments to maintain normal intracranial pressure(64).

Controversy still surrounds the precise pathogenesis of the syndrome and presently theories prevail which implicate each of the intracranial compartments:Blood, Brain and CSF;and postulate that PTC may arise from any one or more of the following mechanisms:

1)An increase in cerebral blood volume.

2)swelling of the brain itself.

3)An increase in CSF production or a decrease in CSF absorption.

Each of these mechanisms is discussed in turn,highlighting some of the relevant work which has led to these various hypotheses.

11.1. Cerebral blood volume:

Cerebral blood volume is affected by homeostatic mechanisms controlling cerebral blood flow.These regulatory properties enable brain perfusion to remain stable when blood pressure or intracranial pressure changes and it is maintained partly through myogenic control of arteriolar resistance.Loss of this autoregulatory control can potentially result in an increase in intracranial pressure(64).

There is little evidence to support an increased cerebral blood volume being an important mechanism in the pathogenesis of PTC.

In 1937,Dandy (46) collected 22 patients with PTC in whom a space occupying lesions had been excluded.He treated these patients with subtemporal decompression to alleviate the symptoms of raised intracranial pressure.Thereafter,for several years,he made a clinical assessment of the intracranial pressure simply by inspecting the site of decompression,noting the degree of distension.He made the observation that the decompression was almost never consistently at its maximum distension but would be intermittently distended with the raised pressure coming and going "with surprising rapidity".He surmised that these rapid fluctuations observed over the decompression site were due to changes in the intracranial vascular bed,which he ascribed to an abnormality in vasomotor control.

Since then,more direct and specific techniques of assessing cerebral blood volume and flow have been employed by various workers.Nevertheless,the evidence supporting an increased cerebral blood volume as a cause of PTC remains inconclusive.

For example,Raichle and co-workers (65) found a 33% mean increase in cerebral blood volume in their 14 PTC patients.However this increase was calculated as equal to a 1% increase of intracranial contents.They noted that a 5% increase in intracranial contents is needed to sustain an elevation in intracranial pressure experimentally.Therefore,they concluded that a blood volume increase is not a major cause of the syndrome.

The limited data to assess blood volume and flow in Pseudotumor Cerebri are conflicting but tend to indicate a small increase in blood volume and a slight reduction in blood flow (66)(67).

Part of the problem pertaining to cerebral volume studies relates to the fact that any increase in cerebral blood volume in patients with PTC may well be a non-specific regulatory response to any increase in intracranial pressure (including that eg. secondary to the presence of a mass)(31).Not enough is known about regulatory changes in cerebral blood flow secondary to various stresses.This is compounded by the fact that additional factors such as measurement artifact;alteration of blood-brain permeability by the use of hyperosmolar contrast media (65);and secondary circulatory changes which may accompany anaesthesia of trial patients;all serve to hinder the interpretation of the results of these studies.

Added to this are studies which refute the role of cerebral blood volme in PTC.Brooks et al (68) measured cerebral blood flow,cerebral blood volume and cerebral oxygen utilization with the technique of positron emission tomography in 4 patients with active Pseudotumor Cerebri and found that these did not significantly differ from controls and could find no evidence of any deterioration of cerebral oxygen utilization or alteration of cerebral haemodynamics.

11.2. Cerebral oedema:

The accumulated evidence suggesting that cerebral oedema is an

important pathogenic factor in PTC dates back more than fifty years and this concept still receives support.
Early reports (1936) describe the finding of a swollen "wet brain with bulging subarachnoid spaces" at surgery (6) and a "bulging brain" seen at subtemporal decompression (46).Similar descriptions of a "swollen cortex" noted at decompression are also to be found in Sahs's series (8).

In an often quoted study,in 1956,Sahs and Joynt (8) did cortical biopsies on ten patients with PTC and concluded that there was extracellular and intracellular oedema.They described a "spongy appearance of the brain with perivascular spaces swollen with intracellular and extracellular oedema scattered throughout the entire white matter giving it a cheesy appearance".Furthermore one of the patients with cerebral oedema on biopsy was subsequently shown to have patent cerebral venous sinuses.In another in whom superior sagital sinus thrombosis was proven on venography to be the cause of the syndrome,the biopsy revealed swelling which resembled that seen in the other cases.The authors conceded that biopsy tissue must be accepted with reservation because of the small amount of tissue and the inevitable distortion that accompanies handling such tissue.However they go on to express confidence in the validity of their findings.

This particular study is important because the findings are unlikely to be corroborated by a repeat study as patients with PTC generally have a good response to appropriate treatment,and the risk of cerebral biopsy in such a group could not be

justified for trial purposes.

The evidence presented for cerebral oedema in PTC in all subsequent studies is indirect and cicumstantial.

In one such study,Raichle (65) provides indirect evidence for the presence of cerebral oedema in patients with PTC.
He showed that the raised intracranial pressure in these patients was associated with a significant reduction in cerebral blood flow and an increase in cerebral blood volume.He attributed the decrease in cerebral flow to tissue swelling as a result of an increase in tissue water content.He did this by virtue of the fact that his measurements of cerebral blood flow were recorded per unit mass of cerebral tissue.Therefore,with this technique any increase in tissue volume uncompensated by an increase in vascular density would be reflected as a reduction in cerebral blood flow through the vascular compartment.However the argument that brain swelling accounts for his findings only holds if alternate explanations for the reduction in cerebral blood flow are ruled out.
Raichle felt that this reduction in cerebral blood flow was not due to impairment of autoregulation,as he demonstrated that cerebral perfusion pressure did not approach the lower limit required to maintain autoregulation.His findings also did not support an increase in cerebral vascular resistance as a possible cause for the decreased cerebral blood flow.Lastly,as previously mentioned,he calculated that his finding of an increase in cerebral blood volume in these patients could not account for the

increased intracranial pressure observed in this syndrome.He speculated that altered cerebrovascular reactivity at the capillary venule level is linked to permeability changes resulting in vasogenic oedema.

The presence of small ventricles,when carefully measured on CT scan (69)(70),supports the concept that the elevated intracranial pressure results from brain swelling.

The very nature of this brain swelling merits further comment. The primary characterictic of cerebral oedema is an increase in the brain water or fluid which leads to the increase in brain volume.In those cases of cerebral oedema which are classified as "vasogenic" this is the result of alterations in the movements of water and solutes across the blood-brain barrier and through the extracellular space of the brain.

It has been suggested,by those who favour the concept that cerebral oedema is of prime importance in PTC,that the trigger for this oedema is a toxic or an allergic response of the nervous system or alternatively a water and electrolyte disturbance governed by hormonal factors.

Some of these interesting endocrine,metabolic and presumed allergic or toxic disorders which have occurred in association with PTC are briefly described below:

A number of authors have quoted the association of this disorder occurring in patients with Addisons disease.However scrutiny of these case reports (14),(15) reveals the

development of cerebral oedema with raised intracranial pressure in ill patients in Addisonian crisis (some of whom died) rather than the characteristic clinical picture associated with PTC.

Although endocrine dysfunction has been suspected in PTC because of the association with obesity,abnormalities of the female reproductive system,and steroid withdrawal,endocrine studies in this syndrome have been unrevealing.Dandy (46) did an extensive endocrine work-up in 15 patients with PTC.They included diurnal cortisol,ACTH stimulation,urinary ketogenic steroids,metyrapone response,cortisol response to insulin hypoglycaemia,basal prolactin and levels of FSH and LH as well as diurnal temperature regulation and all these studies were normal.Likewise Johnson and Paterson (20) found no consistant abnormalities in adrenal function.On the other hand,Barber and Garvan (71) found normal resting cortisol levels but an impaired response to stress (viz:hypoglycaemia).Likewise,Human Growth Hormone response to hypoglycaemia and LH response to GnRH were also thought to be abnormal in some of their patients.These authors concluded that evidence of hypothalamic-hypophyseal insufficiency was present in 7 out of 8 of their patients with PTC.This claim has not been substantiated by other authors.

Dees (72) described the development of this syndrome in three children on prolonged steroid therapy for severe asthma.Sugar and Grant (16)(17) reviewed the cases of PTC which occurred in association with hypoparathyroidism and attributed the cerebral

oedema to a nonspecific "electrolyte disturbance" the most characteristic being the serum calcium.

In support of a possible toxic or allergic trigger for the cerebral oedema there are numerous reports of the syndrome following or occurring simultaneously with a variety of infections as previously mentioned.

If cerebral oedema is an important factor in the pathogenesis of PTC then it appears that it may arise from a number of different causes.The blood brain barrier is not freely permeable to water and certain central neuroendochrine influences (mediated by Noradrenalin,CAMP and vasopressin)have been reported to be important in the regulation of its permeability (70)(73).

Cytotoxic oedema is another category of brain swelling that occurs but is **unlikely** to be a factor in PTC.This type of oedema occurs as a result of the failure of the cellular sodium pump,as in anoxia, and is associated with diffuse brain dysfunction and a grossly abnormal EEG.

An objection which has been raised to attributing the cause of increased intracranial pressure,in patients with PTC to oedema or brain swelling,is their remarkably well preserved conscious state.

However,the presence of extracellular or "vasogenic" oedema may be associated with normal levels of consciousness and a relatively normal encephalogram (70)(74)(75).Some workers believe that it is only when secondary factors such as tissue tension gradients,brain shifts and reduced cerebral blood flow come in to

operation that neurological function is impaired.

11.3. Diminished CSF absorbsion:

The only condition where increased CSF formation has been demonstrated in patients is choroid plexus papilloma.This potential mechanism for PTC remains unproven.

Under normal conditions CSF exists in dynamic equilibrium with absorption matching production.A condition which results in decreased CSF absorption will result in translocation of CSF through the foramen Magnum to the distensible spinal subarachnoid spaces to compensate for the increased intracranial volume and thus prevent a rise in the intracranial pressure.The loss of this compensatory mechanism can lead to a marked elevation in intracranial pressure.

The concept of compliance is helpful in the understanding of these compensatory mechanisms.Compliance is the ratio of the change in volume to the resulting change in pressure (64).At normal intracranial volumes the intracranial pressure is low and remains so with added increments in volume.Thus compensatory mechanisms are adequate,and compliance is high.However as the volume increases,compensatory abilities are exceeded and further addition of volume is reflected in great increases in pressure (64).

A number of good studies have demonstrated impaired CSF absorption with increased resistance to drainage in patients with

PTC. In these studies a variety of different techniques were used to measure CSF absorption, including plasma uptake of labelled albumen (70)(76); isotope cisternography and ventriculography (77); constant infusion manometric testing (78)(79)(80) and a servocontrolled variable rate infusion technique (81).
It is argued that the impaired CSF absorption leads to an increase in the CSF volume which contributes to the raised intracranial pressure.
At this point it is worth considering the controversy of the ventricular system in Pseudotumor Cerebri.

The Ventricular System in PTC:

The controversy concerns the argument that if patients with PTC have impaired CSF absorption with increased CSF volume resulting in raised intracranial pressure, then this would invariably lead to dilatation of the ventricular system. Both sides to this controversy are briefly discussed.

Authors whose studies have shown impaired CSF absorption (77) in PTC argue that the absence of ventricular dilatation did not negate their hypothesis that there is increased CSF volume in PTC. Simultaneous lumbar and ventricular pressure readings were equal providing evidence of free communication through the CSF containing spaces. As the CSF is patently freely communicating in these CSF containing spaces, they maintained that any increase in fluid volume will be accumulated primarily in the capacious and physically most distensable part viz. the subarachnoid space. As the entire subarachnoid

space is available to accumulate an increased CSF volume,no gradients will develop between different parts of the system.Therefore they argued that a relative obstruction of CSF absorption across the arachnoid villi due to either increased resistance in the villi or to a increase in sagittal pressure altering the differential which controls CSF absorbsion will not result in ventricular dilitation.The authors suggest that the production of CSF continues possibly at a slightly reduced rate causing increased CSF volume.Increase in intracranial pressure helps to restore the gradient across the villi to balance the increase sinus pressure or resistance within the villi (77).The CSF absorbsion control system is therefore reset with an increase volume and an increase in intracranial pressure secondary to an impaired absorbsion mechanism.They further suggest that factors known to be associated with PTC such as venous sinus thrombosis reduce absorbsion by increasing the saggital pressure and factors such as Vit A,tetracycline and non-specific infections reduce reabsorbsion by increasing the resistance across the arachnoid villi (77).

The above argument concerning the failure of the ventricles to dilate in PTC remains open to criticism as other conditions with increased intracranial pressure and increased resistance to CSF outflow are characterised by hydrocephalus.Dandy observed that the protruding brain seen at the time of the decompression operation is scarcely relieved by evacuating the fluid from the subarachnoid spaces over the temporal lobe.He

reasoned that if the CSF was increased in volume,the ventricular space would ultimately participate and therefore be enlarged.

Reid et al (69) showed that measurement of the volumes of the lateral and third ventricles by non invasive CAT-based techniques in patients with PTC were significantly lower than controls matched for age and sex.As the ventricles are in direct communication with the subarachnoid space,the existence of smaller than normal ventricles argues strongly against the primary disorder being an obstruction of CSF absorption at the level of the arachnoid villi.In a subsequent paper (70) they present some evidence suggesting that resolution of symptoms in their group of patients was accompanied by larger final ventricular volumes.

Added to this argument about ventricular size in the "impaired CSF absorption" studies are other considerations which should be taken into account.In these studies,pressure measurements are certainly subject to artifacts and error such as anaesthesia induced CSF or venous pressure artifacts,occult leakages, and normal fluctuations in pressure gradients between CSF and sinus blood.Also,concurrent change in the cerebrovascular compartment could introduce measurement artifact suggesting abnormalities in the CSF system.

Accumulated evidence presented thus far,both supports and undermines each of the popular contentions that either cerebral oedema or impaired CSF absorption is responsible for PTC (82).One

view is that more than one pathogenic process is operative simultaneously and that a disturbance in one cerebral compartment will invariably produce a disturbance in another.

11.4. "Dynamic Interplay" theory:

More recently,Gjerris et al (83) measured intracranial pressure,Conductance to CSF outflow (viz:the reciprocal value of resistance to CSF outflow) and cerebral blood flow in a series of 14 patients with PTC.They found a very low CSF conductance to outflow and normal cerebral flow in their patients,supporting the conclusion that decreased CSF flow is of pathophysiological significance in patients with PTC.They propose that patients with PTC,regardless of the different possible causes of the condition,have a common cerebral defect which causes an increased cerebral volume (due to interstitial oedema or alternatively increased cerebral blood volume) as well as a defective CSF absorption.This combination of defective CSF absortion and a "stiff" brain prevents dilatation of the ventricular system.They argue that patients with PTC have two fundamental defects - a defect in CSF absorption and an increased cerebral volume and that this non-compliant combination counteracts dilation of the ventricular system.

Donaldson (84) suggests that PTC is not due to a static increase of one component of the craniovertebral box but involves the hydrodynamics of CSF flow.Ambient CSF pressure depends on the venous pressure in the superior sagittal sinus,the inherent

resistance of the arachnoid villi to the egress of CSF,the rate of CSF formation and the elastic properties of the brain and blood vessels and the capacity of the spinal subarachnoid space to expand.It is possible that the dynamic interplay between each of these determinants of CSF pressure may be disturbed resulting in this syndrome and one or more of these factors may be responsible in any one patient.It seems unlikely that a single pathophysiologic explanation applies to all patients with this syndrome,a conclusion reached by Dandy as far back as 1937.

There remain more speculations than data available regarding the pathophysiologic characteristics of PTC and the limited data available do not allow any firm conclusions.

12. MANAGEMENT OF PTC:

When clinical evaluation of a patient with PTC reveals a specific causative factor treatment should be directed towards correction of that factor.However in many patients no definitive causative factor can be detected and many of the known causative factors have no specific treatment.No controlled studies have been done to show whether weight reduction will result in remission in obese patients.Newborg (85) reported remission with weight reduction in his group of patients but it is not known how many would have remitted spontaneously.Patients in whom PTC develops following vitamin A abuse generally have a remission after stopping further intake of the vitamin tablets (11).

A number of factors preclude an assessment of the comparative efficacy of the various forms of treatment.The assessment is hampered by the limitations of a retrospective analysis in which the patient sample is not controlled.Patients were treated in different departments within the hospital and clinically assessed by different doctors.With regard to the medical therapy there was variation in the indications,dosages and duration of the treatment.In addition CSF pressures and persistent symptoms such as headache were not consistently recorded at follow-up in the eye clinic as attention was primarily directed at determining visual impairment.Taking this into account as well as other factors such as the size of the series,the limited period of follow-up and the natural history of the syndrome (with a tendency for spontaneous remission to occur) it is clear that in the present series meaningful comparisons of the effects of

various forms of treatment cannot be made.This in no way implies that the various treatment modalities did not influence clinical outcome.

No prospective study comparing the various treatments has been done.The fairly high spontaneous remission rate makes evaluation of treatment even more difficult.In addition,the clinical indications for the various therapeutic options have not been clearly defined.Treatment is aimed at relieving symptoms and preventing permanent visual deficits.As the syndrome may have a varied clinical course and prognosis more than one treatment approach may be indicated.The treatment modalities are discussed below:

12.1. Monitoring of visual parameters:

The need for careful monitoring of peripheral fields cannot be overemphasized as loss of vision which may be irreversible is the only serious complication of PTC.Visual acuity reflects foveal function and does not indicate the state of preservation of either the paracentral or peripheral fields.Changes in visual fields are the major guides to therapy (31).Visual fields may constrict severely before the patient notices any loss of vision.Since visual loss may be insidious and often asymptomatic for long periods of time visual disaster can only be anticipated by monitoring visual fields and acuity.Repeated quantitative perimetry is the cornerstone of long term treatment of patients with PTC (26)(55).Best corrected visual acuity should be recorded carefully at each visit and colour vision should be checked.

As PTC may be chronic in some patients it is important to observe each patient at frequent intervals for at least one year after resolution of headache and yearly thereafter,to monitor for the recurrence or for late impairment of vision.Photographs of the fundus may helpfull for comparison.

12.2. Role of visual evoked responses:

Visual evoked responses (VER) are reported not to be a sensitive measure of changes in vision and cannot be used successfully to monitor the course of PTC (31).However in a prospective study of 20 patients with PTC,Krogsaa et al (27) showed a significant increase in VER latencies in the single patient who went on to develop optic atrophy before any changes in acuity or field defects were observed.The VER latencies increased to higher pathological values during the development of field defects before the optic atrophy became apparent.On this tenuous evidence based on their findings in one patient,they suggest that repeated examinations of visual evoked potentials in patients with PTC may be a sensitive indicator of potential visual failure.

12.3. Repeated Lumbar Puncture:

Serial lumbar punctures have a definite role in the treatment of PTC.In many cases the disease is self-limited and undergoes spontaneous remission. These patients should still be followed-up carefully in the future,for visual impairment or the rare instance of delayed emergence of a mass (31).

Half the number of patients (15/30) in this series received 3 or

more lumbar punctures.

Although there is often transient relief of symptoms after lumbar puncture it is not clear to what extent this procedure serves the therapeutic purpose as usually about 30mls of CSF is drawn off to lower the intracranial pressure and this quantity would be replenished within about one and a half hours.Surprisingly patients often note improved symptoms for some days after a single lumbar puncture.There are two possible explanations for this.Firstly,a persistent CSF leak may be produced that seals off in several days and allows the symptoms to reappear.Secondly, transient relief of the elevated pressure may allow some compressed intracranial structures to reassume their baseline shape.Prolonged or unusually high pressures are needed to produce distortion (11).

At the very least serial lumbar punctures appear to be useful early in the treatment.Remissions not infrequently occur soon after presentation and lumbar puncture would show this.Likewise,as treatment is directed at lowering intracranial pressure,this pressure should therefore be measured if treatment is shown to be truly effective.Funduscopic pictures are unreliable as a means of follow-up as papilloedema resolves slowly and one may feel that pressure is dropping as a result of treatment when in fact it is being maintained at relatively high levels (86).Hoffman argues that no cardiologist would consider treatment of systemic arterial hypertension with antihypertensive drugs without monitoring the blood pressure,yet some neurologists will undertake treatment of intracranial hypertension without any

reliable index to gauge treatment effectiveness (86).CSF pressure is the only reliable indicator of persistently raised intracranial pressure.
It has been suggested that lumbar puncture should probably be repeated at least once before starting any other form of therapy except in cases with rapidly failing vision (11).

12.4. STEROIDS:

Steroids were used as part of the medical treatment in approximately half the patients in this study.

The literature is inconsistent with regard to the effects of steroids on CSF formation.The evidence suggests that steroids do not have a significant effect on CSF formation or absorption.The therapeutic effects of steroids on raised intracranial pressure are considered to be secondary to their anti-oedema effect, chiefly via their beneficial effects on endothelial cell permeability rather than any direct effect on CSF formation. There is no properly controlled study evaluating steroids in this condition.However there are numerous reports of the successful treatment of PTC with corticosteroids.Paterson (9) reported the treatment of six patients with steroids (20 to 40mg of prednisone/day) and noted a rapid response in 4,a slow improvement in 1 after 6 weeks and no response in 1 patient. However this was not controlled,the indications for steroid treatment are unclear and the study includes a group who did equally well on repeated lumbar punctures.Hooshmand (87) used steroids in PTC with good effect but did not describe the

indications for its use.Guidetti (24) failed to show a significant difference in outcome in 29 patients treated with steroids or ACTH compared to treatment with diuretics,acetazolamide or glycerol.Once more the study was uncontrolled and the indications for the choice of treatmeant are not specified.In contrast, Weisberg (1) felt that his study provided good evidence for the effectiveness of steroids in this disorder.In 15 patients who did not respond to repeated lumbar puncture in the first two weeks and were then treated with steroids (20 to 50mg prednisone per day or dexamethazone 6 to 12mg daily) it was noted that 13 patients responded to the treatment and the medication was stopped within two weeks without any recurrence.There were also 35 patients who received steroids ab initio together with repeated lumbar punctures and had a good response within a week.When the steroids were discontinued after two weeks the syndrome did not recur.This group includes those patients who may have remitted spontaneously or responded to repeated lumbar punctures alone.In this study all patients who responded to steroids showed an improvement within four days and the medication could be stopped within two weeks.No patient in this series with PTC who did not show a response to steroids in one week subsequently improved on a more prolonged course of steroids.Another case report (31) in the literature described a good response to steroids,but when reduction of steroid dose was attempted after a few months,the syndrome rapidly re-emerged.These authors felt that the steroids should be discontinued after 2 weeks regardless of the response in order to

minimise side effects and prevent possible long term perpetuation of the syndrome related to elevated levels of exogenous steroids,suppression of endogenous production of steroid and the withdrawal of exogenous steroids.Other reports advocating the use of a short course of steroids for the condition claim that most patients begin to respond within 24 hours (86).
From these studies it appears that steroids may be beneficial and improvement is usually seen within a week.At least in some patients tapering the steroids off after two weeks will not result in a recurrence (11).

12.5. DIURETICS:

12.5.1. Acetazolamide:

Acetazolamide is a carbonic anhydrase inhibitor that reduces CSF production. 27% of patients in this study received acetazolamide as part of their medical treatment.

Acetazolamide has been used in a few studies as part of various treatment strategies.It was used in 5 patients without success in lowering the pressure or relief of symptoms in doses of 0.5 to 2.0 G daily for two weeks(1).Others have reported unfavourable results possibly related to the fact that regular acetazolamide has a very short half life (11)(47).Some have found that higher doses of between 2 to 4 G daily are required to decrease CSF secretion but this dose is often associated with systemic side effects including gastrointestinal upset,perioral and digital tingling,acid-base imbalance and irritability (48).
With the exception of choroid plexus papilloma,the rate of CSF

formation rarely plays a primary role in the genesis of pathological increases in intracranial pressure.For this reason Fishman (88) argues that drugs such as acetazolamide and furosemide have only a limited place in the treatment of conditions such as PTC and brain oedema.Theoretically these drugs may be useful in the treatment of raised intracranial pressure due to vasogenic oedema because a reduction of CSF formation might facillitate the drainage of oedema fluid from the oedematous cerebrum to the ventricular system.

Rubin et al (89) found that under controlled conditions of regulated intracranial pressure,acetazolamide administered intravenously was found to decrease CSF production in their small group of patients.The degree of response varied in individual test subjects and the maximum response was always achieved within the first 90 minutes and the duration of the response was no longer than 30 minutes.However, intravenous acetazolamide may cause an acute transient increase in intracranial pressure even while inducing a decrease in the rate of CSF formation.This pressure change is probably secondary to the effects of carbon dioxide accumulation in cerebral tissue,resulting in vasodilatation and a secondary rise in intracranial pressure (88).Experimentally it is apparent that acetazolamide does not significantly inhibit CSF production until over 99% of carbonic anhydrase activity in the choroid plexus of rabbits has been inhibited (90).

In discussing the use of acetazolamide,Ahlskog (11) stated that Lubow and Kuhr had used the long-acting form and claimed good

effect and concluded that if acetazolamide is used,it should probably be used in the time-release form.

12.5.2. Furosemide,chlorthalidone,and the thiazide diuretics:

Furosemide decreases CSF formation by what appears to be interference with chloride transport rather than a direct effect on carbonic anhydrase.Experimentally the use of both furosemide and acetazolamide together reduce CSF formation by 75% in rabbits.Although furosemide and some of the thiazide diuretics have been used in the treatment of PTC,there is little evidence as to their efficacy.In a non randomised prospective study,Sorensen suggests that dehydrating therapy with furosemide (80mg/day) or Chlorthalidone (100mg/day) in combination with acetazolamide (750-1500mg/day) for a period of 6 to 18 months was effective in controlling symptoms of raised intracranial pressure in the majority of his patients with PTC (49).

12.5.3. Osmotic Diuretics:

Reports in the literature have recommended the use of oral glycerol as treatment for PTC and other causes of raised intracranial pressure (91)(92)(93)(94).Hypertonic intravenous solutions have been used in the acute situation to lower intracranial pressure in PTC while one waits for neurosurgical intervention in the face of rapidly failing vision.Prolonged therapy has its limitations because of deleterious side effects.The effects of these agents on intracranial pressure, causing changes in brain volume,are usually transient because complex mechanisms operate to restore cellular volume to normal.

The prolonged use of oral glycerol for obese patients has the disadvantage of high caloric intake.Nausea and vomiting are often induced by its very sweet taste.Glycerol may lead to an increase in the plasma triglycerides (95).

There is poor rationale for the chronic use of hypertonic fluids either orally or parenterally because the brain adapts to sustained hyperosmolarity of plasma (88).

12.6. Surgical Procedures:

Surgery must be considered when medical treatment fails or in the case of rapidly failing vision.Procedures such as subtemporal decompression and optic nerve decompression have been performed but do not address the underlying problem of increased pressure. Some clinicians still prefer optic nerve decompression as a more direct means to prevent permanent vision loss.Lumbar-peritoneal shunting is widely considered to be the surgical treatment of choice.

12.6.1. Subtemporal decompression:

This procedure is seldom done for PTC in recent years.Earlier Greer (96) and Wilson (97) reported their series who underwent subtemporal decompression for this syndrome.Indications included failure of medical treatment and impaired visual acuity .Despite their successes they had a surgical complication rate of 12% and this included seizures,otorrhoea and brain damage.

12.6.2. Optic Nerve Decompression:

Bilateral orbital optic nerve decompression of the perioptic meninges has been advocated for relief of papilloedema and

threatened visual loss following failed medical therapy (98)(99)(100)(101).

Optic nerve decompression was done one only 2 patients in this study. In one patient the procedure was successful (done to one eye only) but the other patient developed bilateral optic atrophy despite having had a decompression to both eyes. At Groote Schuur Hospital, optic nerve decompression is done on one eye at a time under general anaesthetic. If both eyes have increasing visual loss then the procedure is repeated on the other eye approximately one week later requiring a second general anaesthetic.

In a small series of 5 patients, Knight (99) reports that optic nerve decompression produced resolution of papilloedema in every instance usually over one or two weeks, but that unilateral surgery led to resolution of ipsilateral papilloedema alone (ie. unilateral surgery produced ipsilateral effects only). CSF pressures remained elevated after this procedure in three patients and no mention is made of ongoing headaches. In one case in which these workers did simultaneous bilateral fenestration there was a worrying sudden post-operative visual loss (from R 6/18 and L 6/12 with constricted fields pre-operatively, to counting fingers in each eye post-operatively) but this gradually improved over the ensuing months to 6/9 bilaterally. They suggested that this alarming complication may be due to a disturbance in choroidal circulation either following the sudden fall in intracranial pressure or possibly due to excessive CSF drainage into the orbits. The mechanism whereby optic nerve

decompression reduces papilloedema remains unclarified.The surgical defect acts as a CSF shunt but lowers intracranial pressure only occasionally and then only temporarily.Prehaps the procedure somehow protects the optic nerve from the effects of raised pressure.It is unlikely that any incision slit or incision window in the optic nerve sheath remains indefinitely patent. Perhaps surgery results in adhesions which may protect the nerve from the effects of CSF pressure.Optic nerve decompression may well result in obliteration of the optic nerve dural window and adjacent subarachnoid space by fibroblasts,therebye preventing transmission of raised intracranial pressure along the subarachnoid space to the optic nerve head and allowing for the resolution of papilloedema and field defects (100).
Small uncontrolled series report good results with this technique.Galbraith performed this procedure on a group of patients with papilloedema and progressive visual loss,4 of whom had PTC (101).He showed resolution of the papilloedema but visual deterioration was arrested in only three as one patient had progressive atrophy and loss of visual acuity seven months after the operation.

12.6.3. CSF Shunting:

4 patients received lumbar-peritoneal shunts after failed medical therapy.The procedure was successful in 3 as there was no further visual deterioration thereafter.In the fourth patient the shunt blocked 9 months after insertion and had to be removed and ultimate visual status is not known.
In 1955 Jackson et al (102) reported the value of ventricular or

lumbar peritoneal shunting in ten patients with good results.In seven of these patients the shunts were still working successfully after a year.As the ventricles are normal or small in PTC ventricular shunting is particularly hazardous and lumbar-peritoneal shunting is the logical alternative.Subsequently numerous reports have shown this procedure to be an effective treatment when conservative measures have failed particularly in the wake of deteriorating vision.A lumbar cisternogram is done before shunting to ensure patency of the subarachnoid spaces,especially at the foramen magnum.However shunting is not without risk and may be complicated by malfunction due to blockage of the tube (by eg. omentum or scar tissue),displacement of the tube from lumbar canal or peritoneal cavity,adhesive arachnoiditis and post operative infection along the tubes subcutaneously.

In 1971 Eisenberg et al (103) described their technique and long term results in 34 children who required lumbar-peritoneal shunts.Approximately 50% of the patients did not require any revision of the shunt.They felt that in those patients who required revision of their shunts,they had made small but significant improvements in their technique and their subsequent results may well reflect this.In Weisberg's series all five patients in whom shunts were inserted the result was successful with only one recurrence when the shunt blocked (1).Shunting is generally effective in preventing further progression of any visual loss that has occurred,though visual recovery is less certain (104).

12.7. Management strategy:

As PTC has a variable course and prognosis and no controlled prospective therapeutic trials have been done to assess different treatment strategies,it is likely that more than one treatment approach will be effective.However from the extensive data in the literature on the subject,certain therapeutic principles can be recommended:

Regular monitoring of the visual perameters as mentioned previously is crucial in the management of this syndrome.

Patients in whom vision is impaired or deteriorating should probably be hospitalised for observation.

If the patient has mild symptoms with no visual impairment,then a limited number of serial lumbar punctures should be considered. If the disorder persists in spite of repeated lumbar punctures,or the patient objects to repeated lumbar punctures or if vision becomes impaired then medical therapy should be commenced.

There is evidence to support a short course of steroids for this purpose and a dose of between 40 to 60mg of prednisone daily for two weeks,tapering off the dose over a further 2 to 4 weeks has been recommended (11). If the symptoms and signs are mild,a course of acetazolamide or furosemide or both might be considered in place of the steroids.

Should medical therapy fail with the persistance of severe symptoms or if vision should continue to deteriorate,then surgery should be **urgently** considered.

Lumbar-peritoneal shunting is probably the surgical treatment of choice.

12.8. Management of PTC in Pregnancy:

It was not until Foley (7) reported that 16% of his patients were pregnant at the time of PTC that the association received attention.Digre et al (10) studied a group of 21 patients with PTC in pregnancy and reviewed the literature on the subject.They argued that pregnancy occurs in PTC at about the same rate that pregnancy occurs in the general population.The association of pregnancy with PTC may only be a measure of the fact that PTC affects women of childbearing years.PTC can occur in any trimester,although it usually appears in the first half of pregnancy in the majority of patients.It has been suggested that women with PTC have increased rates of spontaneous abortion (11). However the figures for spontaneous abortion in patients with PTC have not been shown to be significantly different from those expected in the healthy pregnant population (10).Visual outcome for pregnant women with PTC is the same as for women with PTC who are not pregnant.Procedures currently required to make the diagnosis of PTC (eg.Lumbar puncture and CT scan) are not contraindicated in pregnancy.These authors strongly feel that the development of PTC in pregnancy is not an indication for abortion.Almost all the treatment regimens used with non-pregnant PTC patients have been used in the pregnant patient.The major exception is caloric restriction,which should be avoided because of the potential dangers of ketosis on the foetus.There is no contraindication to repeated lumbar puncture.Although the use of steroids has been associated with birth defects in laboratory

animals,this association has not been substantiated in the human.Acetazolamide may be used after 20 weeks gestation;earlier use has been associated with a single report of sacrococcygeal teratoma,but acetazolamide is not a confirmed teratogenic agent.The osmotic diuretics probably should not be used in the second half of pregnancy because of the potential decrease in placental blood flow associated with diminished maternal blood volume.The use of chlorthalidone or the thiazide diuretics is controversial for the same reason.Foetal growth and maternal electrolytes should be followed closely in patients treated with these agents.There is no obstetric contraindication to any of the possible surgical decompression procedures.

13. CONCLUSIONS:

This study has analysed those patients with Pseudotumor Cerebri who were seen in a South African teaching hospital over a seven year period.Some general conclusions are presented here.

The first aim of the study was to analyse the spectrum of patients with PTC.The preponderance of female patients is documented with a male to female ratio of 1:4.The mean age of onset was 29 years with 50% of patients developing symptoms in the third and fourth decade.Possible predisposing factors were recorded in 50% of patients.By far the most common predisposing factor was the use of one or more drugs known to be associated with PTC at the time they developed symptoms.

The second aim was to document the clinical features of this group.Headache (93%) and visual blurring or obscurations (60%) were the most common presenting symptoms.With regard to clinical signs,all patients had bilateral papilloedema,9 patients had VI nerve palsies and 2 patients had lower motor neurone VII nerve weakness which rapidly resolved with treatment.The latter are thought to be false localizing signs.

The third aim was to determine the visual prognosis of this group.52% of patients (in whom objective measurements of visual function at follow-up are available) had a residual visual deficit at last assessment with a mean period of follow-up of 1 year.The majority of these patients (12 out of 13) had impairment of visual function at time of diagnosis.In half of these patients

visual function actually deteriorated from the time of first assessment.

The fourth aim was to assess the forms of treatment that have been used.The need for ongoing careful monitoring of visual fields has been emphasized.The various treatment modalities that were used on patients in this study have been discussed and compared to available data in the literature.

The fifth aim was to review the literature with regard to: comparing the results of other studies to the present one;the pathophysiology of the condition;the treatment of the syndrome;and the visual prognosis of the syndrome. Conclusions regarding these facets have been discussed and the similarities between the present study and others have been analysed.Loss of vision which may be irreversible is the only serious complication of PTC.Visual deficits occurred in a significant percentage of patients in this study.The accurate determination of visual loss utilizing careful methods and sensitive testing of afferent visual function is emphasized. Clinical symptoms and signs did not predict which patients were more likely to have visual impairment at time of diagnosis. However,in this study patients who complained of blurred vision or transient obscurations were more likely to have visual impairment compared to those without these symptoms.

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