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The Pseudotumor Cerebri Syndrome

The condition known most widely as the pseudotumor cerebri syndrome is of diagnostic interest and clinical importance not just to neurosurgeons, but also to neurologists, ophthalmologists and headache specialists. In this book three clinicians with extensive experience of pseudotumor cerebri provide a comprehensive review of the condition, which has also been variously called idiopathic intracranial hypertension, benign intracranial hypertension, and other names over the century or so since it was first recognised. It argues for the grouping of all these conditions under the name of pseudotumor cerebri syndrome on the basis of a common underlying mechanism — an impairment of CSF absorption due to abnormalities at the CSF/venous interface.

Giving a detailed account of the history of the condition, the authors review the development of ideas around some of the more contentious issues, including mechanism, nosology and nomenclature. They then deal in depth with aetiology, investigative findings and strategies, treatment and outcome, based on an extensive patient series and a wide ranging review of the clinical literature. The book concludes with a chapter on experimental studies, considering the possibility of establishing a suitable experimental model to facilitate analysis of some of the unresolved issues, and pointing the way to a more complete understanding of this controversial condition.

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The Pseudotumor Cerebri Syndrome

Pseudotumor Cerebri, Idiopathic Intracranial Hypertension, Benign Intracranial Hypertension and Related Conditions

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Brian Owler
John Pickard
To
Alistair Paterson
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Preface

The syndrome we have termed the pseudotumor cerebri syndrome (PTCS) was first characterized as a distinct clinical entity in the papers by Quincke and Nonne, published a little over a hundred years ago. The condition has subsequently received a somewhat bewildering variety of names and its mechanism has also remained controversial. Moreover, it is probably not as rare as was originally thought. In addition, the insights gained by the study of its pathophysiology and management undoubtedly have more general implications for our understanding of intracranial dynamics in other conditions. For these reasons, and because there has been a considerable proliferation of literature on the subject in recent decades, we thought it would be timely to bring together the later observations with the extensive older literature.

The original intention was to have this book ready for publication in 2004 to mark the centenary of Nonne’s paper which introduced the name ‘pseudotumor cerebri’ for a condition sporadically described during the four decades prior to that paper. Like many such endeavours, the present work took rather longer to complete than initially anticipated. Nonetheless, the belated acknowledgement of Nonne’s paper does signify one of the central arguments of this monograph — that the name he proposed for the condition, a name that has endured despite many challenges, should be retained. The only proposed modification is the addition of the term ‘syndrome’ to embrace the collection of conditions which, in practice, share a common presentation, clinical picture, treatment strategy, and outcome, as well as, it is argued, a common mechanism. Whether this argument is successful must be left to readers to decide, but none would disagree that a consensus on nomenclature is desirable.

We believe that there is a close analogy between PTCS and hydrocephalus. Whether or not they do finally prove to have a similar mechanism, that of impaired CSF absorption, with differences being attributable to such factors as the site and cause of obstruction, the rigidity of the cranium, and other things as yet unidentified, remains to be seen. What is undeniable is that the two conditions
do share a number of common aetiological factors, a similar significant proportion of cases for which there is no recognizable aetiological agent, similar clinical features insofar as these are the manifestations of intracranial hypertension without localization, and a similar dramatic therapeutic response to effective CSF drainage.

The book itself falls into three sections buttressed between brief introductory and concluding chapters. The first (Chapters 2–4) comprises the ‘theoretical’ section, dealing with the history of the condition, the theories on disease mechanism, and the vexed issues of nosology, nomenclature and classification. The second (Chapters 5–9) comprises the clinical section, and has two patient databases — a detailed study of two personal series of Ian Johnston covering approximately 60 years and 270 patients, and a comprehensive analysis of the burgeoning literature on the subject. The third section is a single chapter (Chapter 10) which examines experimental studies pertaining to the condition and has the underlying purpose of drawing attention to possibilities for establishing a satisfactory experimental model of PTCS which would surely help resolve some of the outstanding issues.

The three authors are closely linked, not only by their interest in the condition, but also personally, having worked together in different combinations in the three units whose patients are featured in the clinical chapters: the Institute of
Neurological Sciences in Glasgow, the neurosurgical units associated with the University of Sydney, and the neurosurgical unit at the University of Cambridge. During our long association we have become indebted to many colleagues, both clinicians and researchers, within our own units and elsewhere. Because so many people have been involved we have decided, with regret, that they are too numerous to mention individually, but our debt is substantial. Individual mention must, however, be made of Alistair Paterson (pictured) who might justifiably be regarded as the instigator of this study which started more than thirty years ago and is still continuing. We are very happy to be able to dedicate the book to him as a mark of our enduring gratitude. We are also especially grateful to Peter McCluskey, Scott Dunkley, Marek Czosnyka, Nicholas Higgins and Nicholas Sarkies who have each made specific contributions to several of the chapters in relation to their respective specialties. Richard Barling and Rachael Lazenby at the Cambridge University Press deserve our thanks for their interest in this somewhat esoteric field, and their help generally with the project, not to mention their tolerance of the delay in delivery of the manuscript.

Finally, our hope is that this monograph might play a role in resolving some of the key issues in the continuing debate on this intriguing condition. At least it should provide an up-to-date summary of what has become a very substantial literature on the subject. To this end we have made the bibliography extensive, including papers not specifically referred to in the text but included in collected figures or influential in general analysis. We do hope that this monograph will stimulate new work and lead to further advances in the management of this distressing condition for the benefit of our patients.

Ian Johnston
Brian Owler
John Pickard

Life with Benign Intracranial Hypertension
What’s in a name?
I’m angry, cross, annoyed
At a very misguided man
The one who names diseases
With inappropriate, ill suited titles.
Benign Intracranial Hypertension is the label
That doctors place on me.
If I met that man face to face
I would demand that he justify that name.
And tell me what’s benign:
I find the word an insult to my suffering.
It implies it’s OK, harmless, curable,
Slight, superficial, easily treatable.
I know it’s not life-threatening
In a mortal sense,
But it’s killing my living.
I haven’t worked for months
In the job I love,
Had countless lumbar punctures
And needles in other parts.
Operations with tubing and valves
Inserted in unsymmetrical patterns around my body.
Symptoms too numerous to list.
My marriage is under constant strain
And my children suffer,
That really hurts.
Will I be home next week or not?
I want to get on with living,
Have a routine or normality.
Yes, I’m angry all right
What right did he have to label all this benign.
I have a right to be exasperated, infuriated
With his lack of imagination and understanding.
Surely he could have come up with something,
Something just a little more grand,
Something to portray my distress,
To evoke a little understanding in people standing near,
To induce a little sympathy for me.
Come on someone please,
Start now with this disease
Let’s have a renaming ceremony,
But please, remember, invite me.

Liz Galfskiy, Winchester, UK
Introduction

The condition or syndrome to be considered in this monograph has been a clearly recognized clinical entity since the descriptions given by Quincke (1893, 1897) and Nonne (1904, 1914) over 100 years ago. However, reports of cases which were almost certainly examples of the same condition undoubtedly antedated their pioneering accounts by almost four decades. The essential elements of the syndrome are the symptoms and signs of intracranial hypertension without ventricular dilatation and without an intracranial mass lesion. For reasons which will be made clear in the following chapters, we shall call it the pseudotumor cerebri syndrome (PTCS) although quite a variety of terms have been applied to it. It is a particularly intriguing condition for a number of reasons, as follows:

1. Clinically the condition presents an essentially pure picture of raised intracranial pressure (ICP) without focal neurological disturbance and without investigative evidence of structural disturbance, either focal or general. As such, it is a condition which manifests, in isolation, what is a critical component of many neurological and neurosurgical conditions, i.e. intracranial hypertension, thereby creating a situation in which the pathological effects of this component exist in a pure form.

2. Despite much speculation and numerous clinical and laboratory studies (although clinical investigations are constrained by the exigent circumstances of the condition and laboratory studies by lack of a suitable model) there is still no clear consensus on its mechanism, although the predominant view is that the intracranial hypertension is due to a disturbance of cerebrospinal fluid (CSF) dynamics.

3. In the absence of a clear understanding of mechanism, there is no agreement on the nomenclature. Since the condition was first recognized a series of quite distinct names have enjoyed relatively transient popularity, although only pseudotumor cerebri (Nonne’s coinage) has endured. The use of the other terms has depended, in part, on which specialty was mainly responsible for management and, in part, on which theory of mechanism was in vogue.
Some of the more tenacious examples, in approximate temporal sequence, are serous meningitis, hypertensive meningeal hydrops, otitic hydrocephalus, benign intracranial hypertension, and, most recently, idiopathic intracranial hypertension.

4. Again related to uncertainty about mechanism, there has been notable variation in methods of treatment. As with nomenclature, different treatments have had a period of popularity only to be discarded or replaced as side-effects and complications became apparent or as ideas of mechanism changed. What can be said is that all the major forms of treatment employed over the past century have been effective to a significant degree. This is to judge, at least, by the relatively crude criteria of ultimate resolution of the condition and patient survival without apparent neurological deficit, although persistent opthalmological and possibly psychological disturbances may occur.

The evolution of ideas on these four aspects, and other related points, will be examined in the following chapter on the history of the ‘pseudotumor cerebri’ concept. An attempt will then be made to provide a critical analysis of the different theories of mechanism which will include an examination of the fundamental question as to whether there is, in fact, a single mechanism involved or not. Having come to a conclusion about mechanism, however tentative, the vexed question of nomenclature and the related issue of classification will be addressed. Clearly, if mechanism is securely established, nomenclature may become more logically based. The question of classification will, of course, depend on resolution of the issue of whether there is, indeed, one basic mechanism, or at least one final common pathway, as we shall argue.

These three chapters, on history, on mechanism, and on nosology and nomenclature, comprise the theoretical component of this monograph. At this point a provisional conclusion will be reached that we are dealing with a defined syndrome, the underlying mechanism of which is impairment of CSF absorption at the point of transfer of the fluid from the subarachnoid space into the venous system; that is, at the arachnoid villi. The suggestion is, then, that an increase in the fluid component of the intracranial and spinal spaces due to impaired CSF absorption in the face of continuing production at normal rates is the cause of the increase in intracranial pressure, although precisely where and how this excess of fluid is accommodated remains to be determined.

The basic abnormality at the point of absorption may be due to one of three mechanisms:

1. A change in the arachnoid villi themselves
2. A change in the cranial venous outflow adversely affecting the pressure differential across the arachnoid villi on which CSF absorption depends
3. A change in the physical nature of the fluid being absorbed
For each of these three primary causes there exists a number of secondary causes. Despite this multiplicity of causative factors, and the obvious lacunae in our knowledge of how precisely these factors operate, there is a clearly definable clinical entity to which, in the absence of exact delineation of the disease mechanism, a somewhat non-specific but appropriate name should be given. The term ‘pseudotumor cerebri syndrome (PTCS)’, it will be argued, most satisfactorily serves this purpose, at least at present.

In the chapters subsequent to these theoretical deliberations, the practical clinical aspects of the syndrome are considered in chapters following the conventional sequence, i.e. aetiology, clinical features, investigative findings, treatment and outcome. In each of these five chapters a similar format will be followed, beginning with a summary of our own clinical experience based on two substantial series of cases comprising 260 patients investigated and treated in two large centres (the Institute of Neurological Sciences in Glasgow and the Royal Prince Alfred Hospital and Royal Alexandra Hospital for Children in Sydney) over a period of almost 60 years. This will be followed by a detailed review of the literature and conclude with a brief general summary of each section.

With respect to aetiology, one of the more remarkable aspects of PTCS is the large number of putative aetiological agents that have been identified. In many instances, however, the question of whether a particular agent has a true causal relationship to PTCS, rather than being merely a chance association, is not satisfactorily elucidated. Moreover, many of the inculpated agents, whether drugs or other medical conditions, are used or occur very widely, whilst only very few instances of a conjunction with PTCS are recorded. All the supposed aetiological agents will be tabulated and considered, as will the presumed nature of the often somewhat tenuous connection between the particular agent and PTCS in each case. We shall also consider from a practical point of view the issue which bears particularly on the question of nomenclature; that is, whether there are forms of the condition that do arise *sui generis* and might properly lay claim to the title ‘idiopathic intracranial hypertension’, setting aside etymological questions about the term ‘idiopathic’.

In considering the clinical features of PTCS, initial consideration will be given to the rather striking epidemiology of the condition. What is the significance of the uniformly observed preponderance of young obese women in any large series of cases and, in particular, does this have any bearing on the issue of mechanism? In relation to the presenting symptoms and signs, details will be given of their relative frequency and range of severity. Attention will also be directed at two ‘minority’ groups: patients who are diagnosed as having PTCS despite lacking either symptoms or signs of intracranial hypertension, and patients who have symptoms or signs other than those directly attributable to intracranial hypertension.
This latter group bears on the issue of the applicability of the so-called ‘Dandy criteria’, considered in detail in Chapter 4.

In considering the investigation of patients with possible PTCS, the history of the changing pattern of investigative strategies is outlined before considering in turn each of the methods that have been used or are currently in use. Despite this changing pattern, the two key components of investigation have remained the same. The first is the demonstration of raised CSF pressure, whether by direct puncture and simple manometry or by more elaborate monitoring techniques. The second is exclusion of some other cause of raised CSF pressure, now most satisfactorily achieved by magnetic resonance imaging (MRI). As with clinical features, there are issues relating to how rigidly diagnostic criteria should be applied with respect to CSF pressure measurements, CSF composition, and the normality or otherwise of imaging studies which will be considered here. Attention will also be given to another important practical aspect of investigation — how far investigations should be pursued. Specifically, should the role of clinical investigations be simply to exclude conditions other than PTCS, or should they also be directed towards the identification of some causative factor for the PTCS?

The treatment of PTCS remains problematical, and there are still no methodologically satisfactory studies establishing the efficacy of a particular treatment, or properly comparing one treatment against others. There is also the important issue of how vigorously treatment should be pursued in the individual case, weighing up the risks to the patient of continuing intracranial hypertension against those of the treatment in question. The treatments considered are the medical options of serial lumbar punctures, acetazolamide (Diamox®), other diuretics, steroids, weight loss, and a miscellaneous group of other agents used in small numbers of cases, and the surgical options of subtemporal decompression (STD), optic nerve sheath decompression (ONSD), CSF shunting and various direct approaches to cranial venous outflow tract occlusion. It is a striking fact that almost all the treatment methods employed to any extent over the past hundred years, since the disease was first recognized, are still in use. One aspect of the treatment issue, touched on above, is the question of whether therapy can be ‘tailored’ to the individual case, based for example on the degree of severity. Another, and related aspect is what to regard as the ‘end-point’ of treatment, i.e. how important is it to attempt to return the patient’s ophthalmological status and/or CSF pressure to normal, or as close to normal as possible, and as soon as possible? This issue is obviously linked to the natural history of the condition and studies of outcome in treated cases.

Outcome will be the subject of Chapter 9 in which three aspects in particular will be brought into focus. The first is the time course of resolution of PTCS and the relationship of this to its initial severity and method(s) of treatment.
The second is the likelihood of sequelae, especially ophthalmological and psychological sequelae, and how these relate to the severity and duration of the condition. The third is the possibility of error in the initial diagnosis, with some other cause of the intracranial hypertension subsequently coming to light that invalidates the initial diagnosis of PTCS.

The penultimate chapter will consider the various experimental studies that relate particularly to PTCS, and will include a discussion of some of the theoretical issues raised by these studies. Broadly, two groups of experimental studies will be considered. The first group consists of studies of three factors with a well-established aetiological relationship to PTCS — cranial venous outflow impairment, hyper- and hypo-vitaminosis A, and steroids, both prolonged use and withdrawal. All these are factors that have been shown to have the capacity to alter CSF dynamics. Moreover, all of them, and possibly other agents such as tetracycline and its derivatives, offer possibilities as far as establishing an experimental model of PTCS is concerned. The second group consists of various agents which have been shown to have a marked effect on CSF formation, an action which has been assumed to be relevant to the treatment of PTCS.

In the concluding remarks (Chapter 11) the aim will be to summarize the findings and conclusions of the preceding chapters seriatim and, in so doing, to come up with a defensible working hypothesis on disease mechanism, to make a logical recommendation on nomenclature, to bring some clarity to the murky waters of aetiology, to define the basic clinical picture and its acceptable variations, to recommend practical strategies for investigation and treatment, to document the range of outcomes in PTCS, and how these relate to severity on presentation and vigour of treatment, and, finally, to make some suggestions as to how further experimental studies might shed some light on the still obscure aspects of this remarkable condition.
History of the pseudotumor cerebri concept

Introduction

The evolution of the pseudotumor cerebri concept has depended on a combination of precise clinical description and continuing technological advances in the methods used for investigation. Tracing the history of the concept is not only of intrinsic interest but also helps to clarify how our present ideas on disease mechanism, nomenclature, classification, and treatment, all areas of on-going contention, have been arrived at. It must be said, however, that while discussion of the history of ideas on the condition does undoubtedly provide insights into some of its fundamental aspects, it also has the somewhat sobering effect of bringing into focus how little progress has actually been made. For example, on mechanism, the idea of a disturbance of CSF circulation as being at the root of the condition was originally canvassed in the very early years before being discarded, but is now returning to favour. On aetiology, cranial venous outflow impairment, which featured so strongly in early accounts, has now re-surfaced as a major consideration. In treatment, optic nerve sheath decompression, which was initially advocated over 100 years ago before quickly being abandoned, has now returned to a position of prominence. In these three aspects the wheel has turned full circle.

In presenting this outline of history, the papers of Quincke (1893, 1897 (Figure 2.1)) and Nonne (1904, 1914 (Figure 2.2)) are taken as pivotal, signalling the start of attempts to define a specific clinical syndrome. These papers will be given relatively detailed consideration. It is clear, however, that a number of reports of what would appear to be the same condition antedated those of Quincke and Nonne. A general survey of these will be given. Two particular developments of far-reaching significance that were also critical for the recognition of PTCs were first, the invention of the ophthalmoscope by von Helmholtz in 1851 and its application to neurology pioneered by von Graefe, Albott, Huglins Jackson and others, and second, the introduction of the