Annals of Women's Health

Review Article
Published: 07 Dec, 2018

Publications on 'Puerperal Psychosis', 2013-2017

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Abstract

This is a review of 142 works that have appeared in the five years 2013-2017. The relative neglect of this group of psychoses since 1950 has continued, with few case descriptions, investigations or hypotheses about the triggers of bipolar/cycloid episodes with onset soon after childbirth. One new incidental organic psychosis has been reported-herpes simplex encephalitis. There is much to support Marcé's idea that early and late non-organic postpartum episodes are distinct, and his views on the role of menstruation. There are only four active research groups-in Britain, Canada, India and the Netherlands-and there is a need to establish more research programs in populous nations with high birth rates.

Introduction

In 2014, I reviewed 2,452 works on puerperal psychosis [1], and will now extend this by five years. Since What is worth knowing about 'Puerperal Psychosis' went to press, there have been published, to my knowledge, 139 articles, two books and one thesis; the reference list below [2-142] is arranged by year and, within each year, alphabetical order. It is sure to be incomplete, because there will be other theses and articles in unlisted journals. All but seven were in the English language-four in French [29,60,79,89], two in Dutch [72,76] and one in Turkish* [15].

Comparison with Other Medical Literature

Figure 1 compares the number of publications on puerperal psychosis with all medical publications (as represented by Medline citations), and with those on the favoured topic of 'schizophrenia'. For publications on schizophrenia and puerperal psychosis, I have used those listed by PubMed, an index that exaggerates the number by the inclusion of articles with scant relevance, but omits monographs (rare) and theses (which are difficult to find). With these limitations, it is valid for a comparison between diseases (Figure 1).

The Medline citations show a steep increase-in 1950 there were 84,000, in 1999 435,000 and in 2015 870,000; that is a ten-fold increase in 65 years and a doubling in the 18 years from 1999-2015. This increase is due to the rise in population, scientists and journals, and especially the number of nations with research-active universities. Articles on schizophrenia have increased to a similar extent-in 1950 there were 330, in 2002 2,680 and in 2015 5,354; that is a 16-fold increase in 65 years, and a doubling in the 13 years from 2002-2015. The change in publications on puerperal psychosis is quite different. Overall it shows a smaller increment, with only a 5-fold increase since 1950 (56 in the decade 1950-1959 compared with 253 in the last decade). The change is not linear: in the 15 years between 1970 and 1990 there was an increase, followed by a fall, with a recovery in the last 5 years.

I have studied the output on puerperal psychosis in another way-by obtaining the articles and studying them. This inventory of relevant articles starts much further back, and includes a small number of other psychoses related to childbearing-those that start during pregnancy, after abortion and weaning, and later in the first postpartum year. Before 1850 there were less than 5 articles/year, in the next 50 years 10/year, in the years 1901-1950, 15/year rising to 25/year in 1995, falling below 20/year then rising to its present level of 28/year. This confirms the modest increase in articles cited by PubMed since 1950, and (taken back 150 years) shows the same gradual increase. In the first half of the 19th century there were only eight nations involved (Belgium, Britain, Eire, France, Germany, Italy, the Netherlands and USA), to which at least 27 others have been added (Australia, Brazil, Canada, China, Croatia, Denmark, Finland, Hong Kong, Hungary, Israel, India, Japan, New Zealand, Nigeria, Norway, Pakistan, Saudi Arabia, Senegal, Slovenia, South Africa, Spain, Sweden, Switzerland, Tanzania, Tunisia, Turkey and the United Arab Emirates). There can be no doubt that research on puerperal psychosis has lagged far behind other areas of medicine and psychiatry.

The comparison with schizophrenia is interesting. This controversial term refers to a group of

OPEN ACCESS

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Received Date: *24 Sep 2018*
Accepted Date: *29 Nov 2018*
Published Date: *07 Dec 2018*

Citation:
Brockington I. Publications on 'Puerperal Psychosis', 2013-2017. Ann Womens Health. 2018; 2(1): 1013.

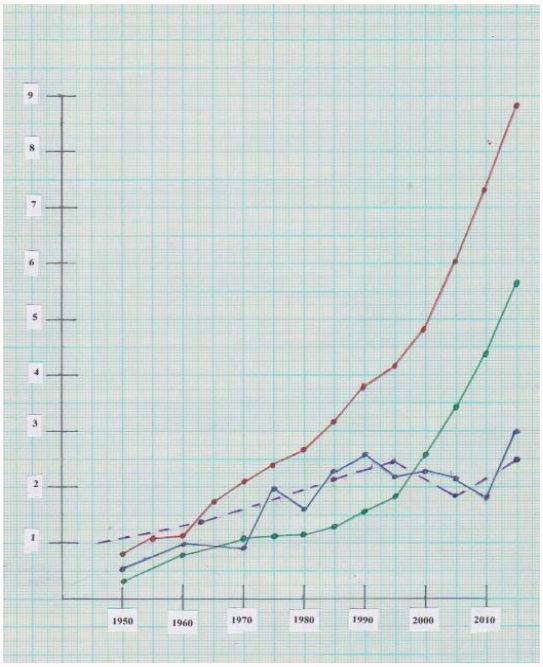

Figure 1: The abscissa shows the years from before 1950 to 2015. The ordinate shows the number of articles as follows:
1) Red, 100,000 Medline citations
2) Green, 1,000 PubMed-listed articles on schizophrenia
3) Blue, x10 PubMed-listed articles on puerperal or postpartum psychosis
4) Mauve (interrupted line), x10 verified articles on childbearing psychoses.

chronic psychoses with no pathognomonic symptoms. At the time of writing (August 2018) PubMed lists 133,242 articles on schizophrenia and 1,152 on puerperal psychosis, a ratio of 116:1; in 1990 when interest in puerperal psychosis was at a peak, it was 60:1. The relative frequency of these two disorders, at their first hospitalization, was examined in a unique first-admission survey [143]: among 161 first admissions, there were five mothers admitted with acute puerperal psychosis. The number of cases of schizophrenia varied between 3 and 45, depending on definition; ten met the Feighner et al. [144] criteria, which emphasized chronicity, selecting patients similar to those that meet modern DSM criteria; this is a ratio of two schizophrenia to one puerperal psychosis. It is not clear why psychiatrists should focus so much more attention on a heterogeneous collection of chronic disorders, to the disadvantage of a group causally linked to an event (childbirth), who's physical and psychological effects are complex, but well understood, and which can be precisely located in time. It is understandable that researchers should devote time and money to chronic psychoses, because of the great expense of caring for them. But puerperal psychoses are important for other reasons-they disrupt young families at a critical time and sometimes lead to suicide and filicide. Applying powerful new investigatory tools to readily-available chronic disorders is a promising strategy, but exploring the link with reproduction is another valuable design, taking advantage of the opportunity to follow a lead to the causes of psychosis. The ratio of publications (100:1) seems inequitable.

There is a school of thought that considers that there is no such entity as 'puerperal psychosis' [47], but that pregnancy and the puerperium can trigger psychotic episodes in a variety of organic and non-organic disorders; when making a diagnosis, it is only necessary to specify the clinical syndrome and indicate the presence of the underlying disorder. This is fair comment, and can best be implemented by biaxial diagnosis, suggested by Essen-Möller [145]. But the obstetric and gynaecological context should not be limited to the puerperium; it should specify abortion, each trimester of pregnancy, the early and late postpartum period, weaning and menstruation.

National Contributions to Research on Puerperal Psychosis

Historically, Germany and France have made the greatest contributions (Table 1). German academics were a generation ahead of their European colleagues, and their original contributions include Osiander's incomparable description of puerperal mania [146]. German authors have produced much of the work on menstrual and eclamptic psychoses, and pioneered follow-up studies. German nosologists introduced heuristic ideas about the classification of the psychoses, including Meynert's and Amentia [147], Bonhöffer's symptomatic psychosis [148] and Wernicke's description of the cycloid or acute polymorphic psychoses [149]. German authors have provided 870 case descriptions. The French contributions are equal to the German. In addition to those of Esquirol [150] and Marcé [151], there are several pioneering descriptions. Delay et al. [152] undertook a unique investigation, using uterine biopsies. French nosologists introduced the concept of folie circulaire [153] or folie à double form [154]-the germ of the idea of manic depressive (bipolar) disorders-and Chaslin [155] described the organic confusional state. French authors have provided 1,155 case descriptions, more than any other language group. It is therefore disappointing that German and French clinical scientists seem to have lost interest in puerperal psychosis, with only 5 papers between them.

Britain and Ireland have contributed strongly since the turn of the 18th and 19th centuries. English papers have included a clutch of pioneering descriptions-parturient delirium [156], early postpartum stupor [157], eclamptic psychosis sine convulsions [158], postpartum psychosis complicating subdural haematoma [159], Korsakow psychosis [160], premenstrual tension and menstrual relapse of puerperal psychosis [161]. In this 5-year period, Britain tops the list in the numbers of publications (with 22% of the total); in the years 1980-1995, when publications on puerperal psychosis peaked, its proportion was even higher (33%).

The Netherlands has a population of 17 million, and a low birth rate (11/1,000 inhabitants) and can expect less than 200 cases/year. Yet its contribution (relative to births) is far above that of Britain, and has been impressive from the dawn of scientific medicine: in the 16th century, van Forestus [162] reported a case with multiple recurrences. Engelhard [163] published the most detailed obstetric survey, and there have been a series of excellent theses-Van Steenbergen and van der Nordaa [164] and Visscher [165], reporting large series followed long term with detailed case descriptions, Klompenhouwer [166], who noted that 40% of his series follow a course with remissions and exacerbations; latterly Bergink [3] has produced valuable data on treatment and introduced a new causal hypothesis.

The Nordic nations have also made strong historic contributions-the largest series in the literature (until recently) from Trondheim [167], three 19th century works that thoroughly explored the role of infection [168-170], and a number of recent studies based on national registers. With small populations and low birth rates, they rank high in the number of papers produced.

The USA made a brave start. As a small country, the asylums in

Table 1: National contributions.

Nation	Incidence[#]	Total Publications	Publications 2013-2017
Germany[§]	738	510	3
USA	4,186	498	24
France[§]	780	464	2
British Isles	792	453	33
Italy	472	90	3
Canada	396	77	11
Netherlands	187	71	15
India	25,000	35	15
Sweden	120	26	6
All others	>100,000	361	24

[#]The approximate number of cases/year is derived from 1/1,000 x population in millions x birth-rate in thousands.
[§]The numbers listed for France and Germany include other francophone and German-speaking nations.

Philadelphia and New York produced two of the earliest surveys, and pioneered the description of onset during parturition [171]. But its population reached that of Britain by 1850, and is now greater than Britain, France, Germany, the Netherlands and Nordic countries put together; as a nation with huge resources and 4 million births/year, its contributions during the last 150 years have been minor, and continue to be so. As will be seen, 21/24 publications have been reviews or case reports; there are no clinical or long-term studies, no investigations and only one survey (using Danish data).

Although puerperal psychosis was not mentioned in Japanese literature until 1934 [172], Japanese authors have been among the first to recognize two recently discovered organic psychoses-urea cycle disorders [173] and anti-N-methyl-D-aspartate receptor encephalitis [174].

Up until 2013, 59 nations had contributed at least one case report or survey; six more have now been added-the Lebanon [21], Oman [40], South Korea [42], Sri Lanka [27], Syria [9] and Thailand [25]. There are six nations with more than two million births/year who have not, to my knowledge, published on this subject-Indonesia (>5 million births/year), Bangladesh, the Democratic Republic of the Congo and Ethiopia (>3 million births/year), Egypt and the Philippines (>2 million births/year).

Analysis by Subject

The 142 works included 13 clinical and longitudinal studies, 9 surveys, 16 investigations, 31 articles reporting 41 organic cases, 21 articles reporting 41 non-organic cases, 20 articles about treatment, 28 reviews and 18 other articles; the total number adds up to more than 142 because some clinical studies and investigations had illustrative cases, and some articles on treatment were reviews.

Clinical studies

The study of symptoms and their timing (onset and course) is in quest of syndromes, better descriptions and definitions, and eventually an improved classification. This endeavour is fundamental, an essential first stage. All investigations lose their power and cutting edge if the patient group includes more than one distinct entity. Progress was made in the 1980s, when puerperal episodes previously thought be 'schizophrenic' were reclassified as manic, and it became clear that many or most puerperal psychoses belonged to the bipolar spectrum. This led to successful treatment with lithium, and the investigation of female bipolar patients, seeking the postpartum trigger [5,34,56,57,123,131]. But it is a mistake to exaggerate this connection: about 20 other distinct psychoses can have onset during the first two puerperal weeks-at least a dozen organic disorders with a specific link to childbearing, incidental brain diseases, brief postpartum delirium and stupor, psychogenic psychosis, depressive, paranoid or schizophrenic episodes and non-reproductive triggers such as bromocriptine and steroids. These are all rare, but collectively they amount to about one third of psychoses breaking out shortly after childbirth [30,117].

In the last five years, two monographs [30,117] and eleven articles [4,8,16,17,43,47,48,57,66,118,133] have addressed the clinical features, course and classification. The two monographs summarized 4,029 cases from the literature, and presented a personal series of 321 cases, of which 139 were followed for at least ten years: the conclusions were that, on the balance of probability, bipolar/cycloid disorders have not one, but five reproductive triggers and onset groups-early and late postpartum, prepartum, after abortion and after weaning. Early postpartum episodes begin between parturition and the 15th day, and a separate disorder (late postpartum psychosis) begins 3 to 8 weeks after childbirth, probably related to the return of the menses. Puerperal psychoses not only recur during or after later pregnancies (73%), but have a tendency to relapse, with return of symptoms within two months of recovery (28%). One other study [118] reported a high relapse rate during a 9-month period following the index admission.

Surveys

There are nine articles describing studies involving record-linkage [12,44,54,65,98,105,132,134,140]. Six of them used the national registers in Sweden and Denmark; the others used Canadian and Scottish data. National registers are a rare and invaluable resource, but, in the study of psychoses with the complexity of the puerperal group, are limited by their use of hospital diagnoses. Two provided information not previously available: a Danish study [54] showed that pre-eclampsia increased the risk of postpartum admission with psychiatric disorders (not puerperal psychosis), and a Swedish study [140] showed that there was no increased risk after *in vitro* fertilization.

Investigations

These are relatively expensive, involving interviews and/or laboratory investigations. The majority were conducted in the Netherlands (5) or the Cardiff unit in Britain (5). Four of the Dutch studies explored the auto-immune hypothesis for the aetiology of postpartum psychosis [3,28,51,107]; an Indian study attempted to replicate their findings on immune cells [129]. Those from Cardiff were based on interviews with large numbers of women with bipolar disorder [34,56,102,131], studying parity, smoking, sleep loss and childhood trauma, and comparing psychosis rates after childbirth and abortion [57]. There was one molecular genetics study (from India), which found an association between puerperal psychosis and METTL23, a gene concerned with methyltransferase [137]. Among the others [49,71,100], a unique MRI investigation from the Institute of Psychiatry in London [123] focused on parous women with a history of bipolar or schizoaffective disorder: eleven with puerperal episodes had smaller anterior cingulate, superior temporal, parahippocampal, superior and inferior frontal gyri.

Case reports

The description of 72 new cases during this quinquennium

continues the low rate of case-reporting since 1950; but this may be due to the failure to find recent theses-the source of over 25% of cases in the literature.

Of 31 organic cases, 23 were of Wernicke's encephalopathy complicating hyperemesis [14,21,23,29,36,40,50,59,78,80-82,94,136], bringing the total to nearly 200 cases. Once again many had been rehydrated with intravenous glucose without thiamine, and it seems likely that these cases will be reported in increasing numbers, because doctors all over the world seem unable to learn that thiamine (introduced in 1936) must be given to women with pernicious vomiting who present in a dehydrated state; perhaps it should be given parenterally as prophylaxis to all women with hyperemesis. There were four more cases of anti-N-methyl-D-aspartate receptor encephalitis, two during pregnancy [63,142] and two post-partum [62,91]; two had ovarian teratomas. A Japanese review [91] collected ten prepartum and five postpartum cases from the literature. The frequency of these complications suggests that this is not an incidental psychosis [30], but has a specific link with childbearing. There were nine reports of other organic psychoses specifically linked to childbearing-an historic case of infective delirium from Australia [61], eclamptic psychosis in USA [68], two Donkin psychoses from USA and Britain [32,112], the first case of chorea psychosis for many years from Turkey [15], a case of early onset psychosis in Sheehan's syndrome from India [24], another Indian case of cerebral venous thrombosis [88], a subdural hygroma complicating subdural anaesthesia from Spain [46] and an unusual case of psychosis associated with non-convulsive status epilepticus during early pregnancy from South Korea [42]. There were four incidental organic disorders, with no known link to childbearing [33,51,79], for example a cerebral tumor [22]; one of these had not been reported before-a case of herpes simplex encephalitis presenting with psychosis four months after childbirth [79].

The 41 non-organic cases do not include those illustrating the two monographs [30,117]. They report cases with an almost full range of onsets-three post-abortion cases 23, ten with onset during pregnancy [6,26,31,87,120,127,128] (including two Runge psychoses [113]), one starting during parturition [111], a brief postpartum stupor [111], six early [6,20,38,61,74,130] and four late postpartum [27,67] (one a ten-week relapse [72]), and eight with non-reproductive triggers [109]. There is one neonaticide [128], several filicides [72,110] and eight attempted filicides [110].

Treatment

There were 20 publications, of which 8 were reviews [19,64,104,125,135,138]. Bergink's thesis 2 had the best data so far available on lithium treatment, and showed that almost all of 64 patients recovered within three months without ECT. Two enormous record studies-of 1,341,715 American and 319,520 British pregnancies-quantified the low risk of prescribing neuroleptics during pregnancy [93,103].

Reviews

The purpose of reviews is to establish a baseline for future research; they should leap frog earlier reviews. There were 17 on subtopics (for example, Wernicke's encephalopathy [69], bromocriptine psychoses [70,106] and recurrent puerperal psychosis 115); as enquiries become more sharply based, these focused reviews help to indicate the growing point. But there were also five general reviews, with 83 [84], 53 [39], 34 [76], 16 [55] and 5 [60] references. Reviews, which merely scratch the surface, bury the primary observations on which our knowledge should be based. It may be difficult to leap frog a general review of more than 2,400 works [30]; but this is not impossible, because these data, which took over 30 years to collect, are assembled in one place, and scholars are welcome to study them, and confirm the conclusions, or more likely correct the mistakes, adding other works missed, or published since 2014.

Others

There were 18 other articles. Jefferies in Australia wrote three historic articles [38,61,124]. There were three annotations about the value of the concept 'postpartum psychosis' [47,52,90], and an article about its use in American legal proceedings [119]. There was an exchange of letters about the role of pre-eclamptic toxaemia [83,86]. Two articles dealt with animal models [92,121], advocating the involvement of steroid sulfatase deficiency, an enzyme modulating steroid hormone synthesis. There was a case in a man [89]. Other articles dealt with ideas of causation in lay people [73], how psychiatrists deal with postpartum psychoses [7] and the effect on partners and husbands [8]. There was a citation analysis showing abysmal levels of scholarship in those who have written about this disorder [108].

Summary and Recommendations

The growing point

The main point of studying childbearing psychoses is to follow a causal lead, and locate the triggers that unleash psychoses in susceptible women.

The work of clinical observation and classification has clarified this task by showing that 'postpartum psychosis' is a rubric for more than 20 distinct disorders, most of which are rare complications of somatic disorders. In many of them the connection with psychosis is obvious; for example, severe pre-eclamptic toxaemia causes ischaemic lesions in many organs, including the brain. In others, the link is still obscure, for example, why pregnancy and childbirth can provoke epileptic psychoses.

Some of these organic psychoses used to be common: Hippocrates briefly described eight cases of delirium complicating post-partum or post-abortion infections (8/17 female cases in his entire compendium); and in the 19th century eclampsia was common. But in high income nations, even these are now rare. The 'picture puzzle' that still arouses curiosity is the cause of non-organic psychoses, with early onset and without signs of organic disease. Very little progress has been made. While, in the 20th century, almost every area of medicine has made astonishing and revolutionary advances, this group of psychoses can boast of improvements in treatment shared with the rest of psychiatry (neuroleptics and ECT), and the establishment of mother & baby units in a few countries.

- As for the causes, progress in the last 100 years is limited to two confirmed findings:

on-organic psychoses are more common in 1st time mothers, although this is a small effect and applies only to those of early postpartum onset.

- With a shift in nosological boundaries, the link with bipolar disorders became clear, leading to treatment and prevention by mood stabilizers. This association may have been exaggerated: about 40% of affected mothers have the syndrome of mania, and, in my series, 25% had an acute polymorphic (cycloid) syndrome; the study of recurrent

childbearing episodes [30,117] supports the idea that these are interchangeable, but the combined 'bipolar/cycloid' group is still only two thirds of all post-partum episodes.

Clinical studies have offered a further clarification which is not, at present, accepted. Marcé's intuition [175] discovered that postpartum psychoses could be split into early and late forms. In his view, episodes that started in the second and third months, or even later-at weaning-were related to the return of menstruation. There is much to support his views [30]: the distribution of onsets shows a steep fall 15 days after the birth, with a second smaller peak at about six weeks. In the literature, almost 400 late episodes have been reported, about one third of the number with early postpartum onset. Eight mothers in the literature and four in my series [30] had two 4 to 13 week onsets, and surveys have found a raised admission rate in the 2nd and 3rd months after childbirth. As for the association with the return of the menses, this has never been investigated, even though, with radio-immune assay (introduced in 1956) and other gynaecological investigations, the phase of the menstrual cycle can be precisely determined.

As for those with early onset, there is a dearth of causal hypotheses. During the last five years, the role of sleep deprivation [131], steroid sulfatase deficiency [92,121] and auto-immunity [2,3,28,51,107] have been advocated. I consider that the role of menstruation should be investigated, and not only in the late onset group. Abnormal menstruation may also be active in relapses of early puerperal episodes, and in monthly psychoses during early pregnancy (Runge psychoses [113]). Menstrual and puerperal psychoses have similar clinical features and are both complications of the female reproductive process; in the literature and my series, twenty-one mothers have had solid evidence of both, which is evidence that, on the balance of probability, they are associated. It is possible that this association is merely due to their sharing a common diathesis-manic depressive psychosis or a bipolar variant-but the early puerperium is also a time when the menstrual process is released from inhibition. If the menstrual association with late onset postpartum psychosis and relapses is confirmed, the hypothesis that early postpartum episodes are triggered by the resumption of the menstrual cycle is worth investigating.

Recommendations for research

One of the main reasons for the stagnation in the growth of knowledge is the failure to keep up to date with what is known. Citation analyses [108] expose the depth, degree and extent of this ignorance: the mean number of works cited is 8 (0.3% of those written), and the mean for 'reviews' is 9. Much of the best work has been forgotten. It is absurd to plan or fund research without locating the boundaries of knowledge.

It is important to take on board the complexity of this group of psychoses. Organic forms and some non-organic variants may be rare, but cumulatively they spoil the homogeneity of patient groups used in surveys and investigations. Those investigating non-organic puerperal psychosis should eliminate organic causes and non-reproductive triggers, and focus on those with a bipolar/cycloid clinical picture and a particular onset group. I would make three other recommendations:

- That they use state-of-the-art clinical methods, such as multiple information sources, multiple raters and polydiagnosis, in order to match the precision of the investigations (epidemiology, molecular genetics, neuroscience).
- That they recruit mothers followed for several years, with multiple episodes and lifetime diagnoses.
- That they seek to replicate the claims of other research teams.

Epidemiologists could, for the first time, undertake a community survey. With disorders affecting only 1/1,000 births, it would be necessary to screen at least 100,000 mothers, yielding about 100 puerperal psychoses. A second stage, also taking several years, would be spent interviewing those identified, studying their records, documenting their lifetime course, and making diagnoses with the best available clinical methods.

In the study of acute episodes, charting the menstrual process is a priority. Late onset cases deserve particular attention, to find out whether their frequency and timing is affected by lactation, and to refute or confirm Marcé's hypothesis that they are menstrual, not puerperal psychoses, ending years of speculation and uncertainty. Since a substantial minority of mothers with postpartum psychoses relapse, and a few relapse repeatedly, we need to know whether these relapses are related to the menstrual cycle. This is also an opportunity to study the pathogenesis of a psychosis.

Clinical observation is still important. The role of the clinician is not just to pigeonhole patients into a contemporary classification. This may help with management; but medicine has the ambition to prevent disease and every clinician can participate in the search for causal clues. Clinicians should approach those under their care with an enquiring mind, asking, 'What can be learned from this case?

The last five years have continued the disappointing neglect of 'puerperal psychoses'. There is a need to recruit dedicated clinical scientists working in nations with research-active universities and large numbers of cases. These might be found in several countries that have already contributed to this literature-Islamic nations like Turkey, and African countries like Nigeria, Senegal and South Africa.

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