

Prolactin and seizure activity

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SUMMARY Prolactin secretion after tonic-clonic seizures (10 patients), complex partial seizures (five) and non-epileptic attacks (three) was studied in a group of children aged between 0.3 and 14 years. Seven patients with other subcategories of seizure disorders were also studied. Eight children with tonic-clonic seizures exhibited post ictal concentrations of prolactin greater than 500 mU/l. One of the children, who responded on one occasion, did not do so on another. Three children with complex partial seizures had post ictal prolactin concentrations greater than 500 mU/l, while in two the increased values were more modest (390 mU/l and 420 mU/l). The timing of the peak post ictal prolactin concentration varied from less than 20 minutes to a prolonged plateau for three hours. Other seizure types—simple partial with motor signs (2), absence seizure (1), myoclonic seizure (1), minor epileptic status (3) (with one exception), and non-epileptic attacks (3) were not associated with post ictal concentrations greater than 500 mU/l.

Prolactin secretion has been documented during and after certain seizure types in adults.^{1,2} This prompted us to investigate whether or not a similar phenomenon is observed in childhood. The principal clinical application of this finding in adults is the distinction between epileptic and non-epileptic attacks—a problem also encountered in childhood.^{3,4} We examined prolactin secretion after generalised tonic-clonic and complex partial seizures and also non-epileptic attacks. To increase our understanding of the possible mechanism of prolactin secretion, we also investigated patients with other forms of seizure disorders—simple partial with motor signs, an absence attack, a myoclonic seizure, and minor epileptic status.

Patients and methods

Patients with epileptic and with non-epileptic attacks were studied. Clinical details are given in Tables 1 to 4. All patients were on anticonvulsant medication except cases 11, 16, and 22. All but one patient was cared for at the Hospital for Sick Children. The ethical committee gave approval for the study. Classification of seizure type was based on clinical and electroencephalographic criteria in accordance with the Revised International Classification of Seizures.⁵ A description of the seizure pattern was recorded at the time of the attack by one of the authors (AB). The largest group (cases 1–10)

had generalised tonic or clonic seizures, or both. A partial seizure was classified as complex if there was evidence of an alteration in the level of consciousness. The term minor epileptic status has been used as described by Brett,⁶ with the frequency and severity of myoclonic attacks so disabling that the child's mental and physical activities are grossly impaired.

The patient in case 9 was studied in minor epileptic status as well as after an isolated generalised tonic-clonic seizure while not in minor status. Two patients (cases 15 and 23) had a mixture of complex partial and non-epileptic attacks. Four patients (cases 12, 13, 14, and 15) had complex partial seizures with secondary generalisation.

As far as possible, blood samples were taken in the process of other investigations of clinical importance to the child. Blood was taken interictally as a baseline and between 0 and 20 minutes post ictally or 20 minutes post ictally, or both. In two children (cases 3 and 12), samples were taken up to 180 minutes. Studies were limited in the very young or distressed child and performed through the same indwelling cannula when possible in all patients. For this reason five baseline concentrations could not be done.

Serum samples were stored at -20°C . Prolactin was assayed in the Endocrinology Laboratory of the Institute of Child Health using a double antibody radioimmunoassay. The antisera used was a rabbit

antiprolactin PRL2 (St Bartholomew's Hospital). Samples were assayed against a standard International Reference Preparation of Human Prolactin 75/504 from the National Institute for Biological Standards, Holly Hill, London. The normal values for the laboratory are less than 360 mU/l (0 to 1 years) and less than 200 mU/l (2 to 14 years), with slightly higher values in girls than boys.

Case report

This patient (case 15) was a 13 year old boy with a long history of seizures. Separation anxiety and family pathology were complicating features. At 18 months of age he had episodes of transient weakness of his right arm and leg with frequent falls. From 4 years he complained of a 'funny feeling' in his right arm associated with episodes of falling. At 6 years of age he developed nocturnal episodes with tonic-clonic features and was started on anticonvulsant medication. Subsequently the character of the attacks altered and a series of medications was tried. He became increasingly distressed after the attacks. At the time of admission to this hospital he was frightened to leave his home and was extremely anxious whenever his parents departed. He had not attended school for some months and father slept in the same bed in order to 'get him through the night'.

During a lengthy admission to hospital, careful observations were made and two main types of attack identified. One type of attack occurred when the patient was asked to do something he did not want to do and followed protest. It frequently occurred before parental visits or planned trips to his home. A crescendo of distress with panic and palpitations would occur, then he would slip limply onto the floor and his arms would stiffen for periods of up to two minutes. He would often talk during the attack and subsequently recall what was said. Corneal reflexes were present and plantar responses downgoing. The whole attack lasted up to 20 to 30 minutes. He frequently wept after the attack but was able to continue his activities. The prolactin concentration did not rise (Table 4).

In the other variety of attack, precipitants were often, though not always, lacking. He complained of an unusual sensation in his right arm, smacked his lips, asked for a drink, turned his head to the right and upwards, and became hypertonic on his right side and then his left followed by generalised clonic movements. He was not responsive to spoken or physical stimuli during these episodes. They occurred during sleep or waking hours. He often injured himself. After the attack he was drowsy, had upgoing plantar responses, absent corneal reflexes and right sided pyramidal weakness. He became

tearful, confused, and was amnesic for the episode. His prolactin value rose appreciably after these episodes (greater than 1000 mU/l) and baseline interictal values were sometimes high (50 to 400 mU/l). The ictal and interictal electroencephalogram did not show focal signs or definite paroxysmal features and two computed tomograms were normal. The former attacks were seen as non-epileptic attacks more characteristic of an anxiety disorder with panic. The latter were seen as complex partial seizures with secondary generalisation.

Results

The results of prolactin studies are presented in Tables 1-4. Seven children (cases 1, 7, 10, 11, 12, 15, and 19) had raised baseline concentrations for age, and three of these suffered from complex partial seizures (cases 11, 12, and 15).

Eight children with generalised tonic-clonic seizures exhibited post ictal concentrations of prolactin greater than 500 mU/l (Table 1). One child (case 1) had a very high baseline value with a significant rise on one occasion but not on another. Three children with complex partial seizures showed post ictal prolactin concentrations greater than 500 mU/l while in two values were more modestly raised (cases 11 and 14—Table 2).

In seven children (cases 4, 5, 8, 9, 12, 13, and 14) the rise in prolactin occurred early (that is within 20 minutes). In five of these (cases 5, 8, 9, 13, and 14) prolactin was shown to be already falling to lower concentrations by 20 minutes. In two other children (cases 3, and 12) concentrations were more sustained with the increase persisting at three hours.

As numbers were small in each seizure group, sex and age variables were not analysed but responses were seen in both sexes over a wide age range (0.3 to 13 years).

Table 1 Prolactin concentrations (mU/l) in generalised tonic-clonic seizures

Case no	Age (yrs)	Sex	Baseline value	0-20* mins	20* mins	180* mins
1	0.3	M	690		950,675	
2	4	F	175		530,1000	
3	1	F	337		825	550
4	2	F		860	1000†	
5	6	F		960	500†	
6	11	M			175	
7	5	M	345		700	
8	6	M	190	1290,2000	1730†	
9	13	M	95,240	1420	820†	
10	5	M	705	270	245†	

*=Post seizure.

†=Serial.

Table 2 Prolactin concentrations (mU/l) in complex partial seizures

Case no	Age (yrs)	Sex	Baseline value	0-20* mins	20* mins	180* mins
11	7	M	225		385	
			720		395	
12	12	M	525		> 1000	765†
				860	890	
13	11	M	<50	700	<50†	
14	12	M	195	420	235†	
15	13	M	400		> 1000	
			195			
			50			

* = Post seizure.

† = Serial.

Other seizure types (Table 3) were not associated with post ictal prolactin concentrations greater than 500 mU/l and frequently were much lower. The patient in case 9 was the one exception to this. He was in minor epileptic status and had persistently raised prolactin values. Prolactin did not rise to more than 500 mU/l after the three, non-epileptic seizures (Table 4).

In total, 12 tonic-clonic seizures were studied and after two of these seizures prolactin concentrations were not greater than 500 mU/l; that is 17%. Nine complex partial seizures were studied and after three seizures prolactin was not greater than 500 mU/l; that is 33%. Only three non-epileptic attacks

Table 3 Prolactin concentrations (mU/l) in patients with other categories of seizure

Case no	Age (yrs)	Sex	Type of seizure	Baseline value	0-20* mins	20* mins
16	5	M	Simple partial (focal motor with march)	625†		235
17	0.2	F	Simple partial (focal motor with march)	<50		<50
18	11	F	Absence (impairment of consciousness only)	<50		220
19	4	F	Single myoclonic	420		320
<i>Serial prolactin samples</i>						
20	14	M	Minor epileptic status	175, 140, 115, 125		
21	10	M	Minor epileptic status	60, 125, 200, <50, <50		
9	13	M	Minor epileptic status	515, 750		

* = Post seizure.

† = Droperidol (dopamine blocker) given 61 hours previously.

Table 4 Prolactin concentrations (mU/l) in non-epileptic attacks

Case no	Age (yrs)	Sex	Baseline value	20 mins*
15	13	M	400, 195, 50	375
22	12	M		<50
23	14	M	<200	<200

* = Post attack.

were studied, and in all (100%) the prolactin value did not rise above 500 mU/l.

In 21 children with tonic-clonic and complex partial seizures the mean baseline concentration and the mean value at 20 minutes were 378.3 and 709.8 mU/l respectively. In the four children with other seizure disorders (excluding minor epileptic status) these mean values were 286.3 and 206.3 mU/l respectively. Clearly differences with these small numbers are only suggestive of trends and do not reflect the wide standard deviations and the alternations in baseline and response in the same patient.

Discussion

The results in our study are similar to those in adults,^{1,2} but are more tentative in view of the small numbers. They suggest some discrimination between epileptic and non-epileptic phenomena. This was well illustrated in case 15 where the results of prolactin studies gave further evidence that the patient had a mixture of complex partial and non-epileptic attacks.

It is known that prolactin is increased in situations characterised by stress, arousal, and hypoglycaemia.⁷ Certain drugs including chlorpromazine, the butyrophenones, and methyl dopa increase prolactin secretion. Exercise can lead to small rises.⁴ There is also some evidence that patients with generalised seizures may have high baseline values.^{3,4} In addition there is a paucity of information on prolactin values in childhood. To eliminate errors of interpretation from false negative results, we suggest serial blood samples be taken through the same scalp vein or catheter between 0 and 10 minutes post ictally or after a suspected pseudoattack and again at 20 minutes. A serial rise in prolactin or a value greater than 500 mU/l provides evidence that a generalised or complex partial seizure has occurred. It is essential that a detailed record of clinical phenomena be made and that the final decision on the nature of the preceding event is based on assessment of the clinical, biochemical, and electroencephalographic findings. We have chosen 500 mU/l as an arbitrarily high guideline indicative of an appreciable increase in prolactin secretion. More caution,

however, may need to be exercised in the group of children with complex partial seizures, since three of the five children had raised baseline values. The results from the three children in minor epileptic status are difficult to interpret. All the children had multiple seizure types, were mentally retarded, and were also heavily medicated at the time of the study. Clinical phenomena consisted of subtle motor movements and alterations in levels of consciousness that could not be evaluated reliably. Each of the three patients had been in minor motor status for periods of weeks. The critical factors causing prolactin secretion in these situations are not clear.

Electrochemical stimulation of the medial basal hypothalamus in animal models⁸ increases prolactin release. It is thought that abnormal electrical activity may lead to suppression of dopamine (a prolactin inhibitory factor), synthesised in the arcuate and periventricular nuclei of the medial basal hypothalamus, and thus result in a rise in prolactin.⁹⁻¹¹ It is postulated that in complex partial seizures there is spread of electrical activity from medial temporal structures to the hypothalamic nuclei resulting in alteration of consciousness and secretion of prolactin.¹⁰

The association between psychiatric disturbances and epilepsy has been discussed for many years.¹² Adamec and Stark-Adamec¹³ introduced the concept of limbic permeability—the degree of propagation of seizure activity from mesial temporal structures to the thalamic and hypothalamic areas—and noted relations between behavioural disturbances in cats and this phenomenon. Other evidence of prolactin secretion in complex partial seizures^{3 4 10} suggests that prolactin may serve as a biological marker of limbic involvement. Further evidence for this has come from Dana-Haeri:¹⁴ she documented different patterns of hormone release in patients with partial seizures with psychopathology and patients with partial seizures without psychopathology.

There is a need to examine whether or not there are differential patterns of prolactin secretion with and without psychiatric disorders in children with epilepsy. The assessment of other pituitary hor-

mones especially growth hormone release in relation to seizure disorders is another area of interest.

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References

- Abbott RJ, Browning MCK, Davidson DLW. Serum prolactin and cortisol concentration after grand mal seizures. *J Neurol Neurosurg Psychiatry* 1980;**43**:163-7.
- Trimble MR. Serum prolactin in epilepsy and hysteria. *Br Med J* 1978;**ii**:1682.
- Collins WCJ, Lanigan O, Callaghan N. Plasma prolactin concentrations following epileptic and hysterical seizures. *Br J Clin Pract* 1982;**Suppl 18**:191-2.
- Höppener RJE, Rentmeester TH, Arnoldussen W, Hulsman J, Meijers CAM. The changes in serum prolactin level following partial and generalised seizures. *Br J Clin Pract* 1982;**Suppl 18**:193-5.
- Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;**22**:489-501.
- Brett E. Minor epileptic status in children. *J Neurol Sci* 1966;**3**:52-75.
- Noel GL, Suh HK, Stone JG, Franz AG. Human prolactin and growth hormone release during surgery and other conditions of stress. *J Clin Endocrinol Metab* 1972;**35**:840-51.
- Clemens JA, Shaar CJ, Kleber JW, Tandy WA. Reciprocal control by the preoptic area of LH and prolactin. *Exp Brain Res* 1971;**12**:250-3.
- Thorner MO, Logis IS. Prolactin secretions as an index of brain dopaminergic function. *Adv Biochem Psychopharmacol* 1981;**28**:503-20.
- Dana-Haeri J, Trimble MR, Oxley J. Prolactin and gonadotrophin changes following generalised and partial seizures. *J Neurol Neurosurg Psychiatry* 1983;**46**:331-5.
- O'Dea JPK, Gould D, Hallberg M, Weiland RG. Prolactin changes during electroconvulsive therapy. *Am J Psychiatry* 1978;**135**:609-11.
- Gibbs FA, Gibbs EL, Furster B. Psychomotor epilepsy. *Arch Neurol Psychiatry* 1948;**60**:331-9.
- Adamec RE, Stark-Adamec C. Limbic kindling and animal behaviour—implications for human psychopathology associated with complex partial seizures. *Biol Psychiatry* 1983;**18**:269-93.
- Dana-Haeri j, Trimble MR. Prolactin and gonadotrophin changes following partial seizures in epileptic patients with and without psychopathology. *Biological Psychiatry* 1984;**19**:329-36.

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