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Platelet calmodulin levels in adolescent idiopathic scoliosis (AIS): can they predict curve progression and severity?

Summary of an electronic focus group debate of the IBSE

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This paper provides an edited summary of the second electronic focus group (EFG) of the International Federated Body on Scoliosis Etiology (IBSE). It contains the research of Professor Thomas G Lowe MD and his colleagues on platelet calmodulin levels in adolescent idiopathic scoliosis that was debated via e-mail by IBSE members during the period October 2002–July 2003. The summary (Professor Lowe's statement, comments, questions and answers 1–24) was circulated by e-mail to IBSE members on 22 August 2003 and no further comments were received. Ideas presented in this summary are personal opinions and are not necessarily shared by all those within IBSE. The edited summary of the first EFG of the IBSE and some details about the IBSE have been published [19].

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Abstract There is no generally accepted scientific theory for the etiology of idiopathic scoliosis. As part of its mission to widen understanding of scoliosis etiology, the International Federated Body on Scoliosis Etiology (IBSE) introduced the electronic focus group (EFG) as a means of increasing debate of extant knowledge on important topics. This has been designated as an on-line Delphi discussion. The text for this EFG was written by Professor Thomas G Lowe MD and drawn from research carried out by himself and his co-workers on platelet calmodulin levels in patients with adolescent idiopathic scoliosis. To explain the relationship of platelet calmodulin levels to scoliosis curve changes in AIS brought about spontaneously, by brace treatment, or surgery Dr Lowe attributes the platelet calmodulin changes to paraspinous muscle activity and sug-

gests that the calmodulin acts as a systemic mediator of tissues having a contractile system (actin and myosin). Controversy includes: 1) the lack of normal data and the large variability in baseline levels of platelet calmodulin, necessitating the use of the AIS subjects as their own controls; 2) calmodulin is not usually used as a marker of platelet activation; 3) whether the platelet calmodulin changes which appear to reflect an abnormality of a portion of the spine are related to local and/or regional changes in muscles, nervous system, or immature vertebrae. What is not controversial is the need for more research on platelets and the immature deforming skeleton in relation to etiology and prognosis.

Keywords Scoliosis · Idiopathic · Adolescence · Platelets · Calmodulin

Introduction

In the absence of any generally accepted scientific theory for the etiology of idiopathic scoliosis, treatment remains pragmatic and unrelated to such knowledge. The International Federated Body on Scoliosis Etiology (IBSE [19]) introduced the electronic focus group (EFG) as a means of increasing debate of extant knowledge on important topics. The text for this debate was written by Professor Thomas G. Lowe MD based on the important research carried out with his co-workers. The EFG was sent by e-mail to all IBSE members, together with an invitation to send questions by e-mail to Dr. Dangerfield who, as the EFG moderator, collated them and sent them to Professor Lowe for his response. The original paper was then sent again to all IBSE members, together with the questions and answers generated by the first round of the debate. Further submissions were received which necessitated a second round of the debate. Most questions related to specific passages in the original Lowe text. Where this is the case, an extract of the text is reprinted or a précis is given in a series of comments. Each comment is followed by the respective question(s) and then the answer(s) provided by Lowe.

In the early 1980s abnormalities in the structure and function of thrombocytes were noted in patients with AIS [7, 16, 17, 18, 22, 23, 24]. The research of Dr Lowe and his colleagues is predicated on the view that the platelet can be considered a “mini” skeletal muscle with a similar protein contractile system (actin and myosin) so that both would be affected if a systemic cellular defect was present. To explain the relationship of platelet calmodulin levels to scoliosis curve changes in AIS brought about spontaneously, by brace treatment, or surgery, Professor Lowe attributes the platelet changes to paraspinal muscle activity and suggests that calmodulin acts as a systemic mediator of tissues having a contractile system (actin and myosin). The field is new and has engendered controversy, including:

1. The lack of normal data and the large variability in baseline levels for platelet calmodulin levels, necessitating the use of the AIS subjects as their own controls
2. Calmodulin is not usually used as a marker of platelet activation
3. Whether the platelet calmodulin changes attributed to an abnormality of a portion of the spine are related to:
 - a. Local and/or regional changes in muscles, nervous system, or vertebrae
 - b. Pathomechanisms of progressive AIS, and
 - c. Prognosis.

What is not controversial is the need for more research on platelets and the immature deforming skeleton.

Statement by Professor Lowe MD

Platelet calmodulin levels
in adolescent idiopathic scoliosis (AIS):
can they predict curve progression and severity?

Abnormalities in the structure and function of thrombocytes have been noted in patients with AIS by many investigators [7, 16, 17, 18, 22, 23, 24] and reviewed [12, 13]. Because the platelet can be considered a “mini” skeletal muscle with a similar protein contractile system (actin and myosin) it follows that both would be affected if a systemic cellular defect was present. The platelet, unlike skeletal muscle, has no axial attachments making it independent of the secondary effects of the axial skeleton that potentially are produced by the scoliotic deformity. Yarom and co-workers [21] first noted that calcium and phosphorus levels were elevated in skeletal muscle of patients with AIS and subsequently [22] observed that they were also elevated in platelets of the same AIS patients. Some of the platelets were also larger than normal.

Muhlrad and Yarom [17] noted decreased activity of the intracellular contractile proteins within the platelet. They also noted under electron microscopy three distinct types of platelets, reticular, metallophilic and pale cell [25]. The metallophilic platelet was seen most commonly in patients with AIS and was felt to be related to altered cell wall permeability [24]. In another study the same group noted that the platelets from AIS patients were more negatively charged than controls [16].

Calmodulin regulates the contractile properties of muscle and platelets through its interaction with actin and myosin and its regulation of calcium, which transports calcium from the sarcoplasmic reticulum.

Increased calmodulin levels in platelets have been shown to be associated with the progression of adolescent idiopathic scoliosis. Kindsfater et al. [10] compared 17 patients with AIS with varying degrees of curvature with 10 age and sex-matched controls, and found that based on a single determination for each patient during growth, platelet calmodulin levels were higher in skeletally immature patients with progressive curves (10° per year) than those with non-progressive curves and age-matched controls.

This led to a multi-center longitudinal study to determine whether serial platelet calmodulin levels in skeletally immature patients with AIS correlate with curve progression and severity over a period of time [14]. There are 105 patients enrolled in the study and preliminary longitudinal data on 61 patients with AIS. All patients were Risser 0 and premenarchal at time of enrollment. Simultaneous blood draws and standing radiographs of the spine are obtained at 6–9 month intervals. Platelets are isolated from the blood and platelet calmodulin levels are measured using an enzyme-linked immunosorbent analysis. The data have been analyzed from 55 patients with more than 2 evaluations. The data relating calmodulin levels to

curve magnitude were based on 28 patients who were followed without treatment. In the 13 patients with curves that progressed more than 10° per year, platelet calmodulin levels increased more than 100% in all patients. No patients in this group progressed to a point where surgery was recommended. Of the 15 patients with non-progressive curves, relatively little change in calmodulin levels occurred in 11 patients (73%). In the other four there was considerable variation between evaluations that did not correlate with the serial radiographs. The results for both groups were statistically significant.

Of interest, there was a large inexplicable discrepancy between baseline levels of different patients in the series that did not allow for development of a normal range for platelet calmodulin and to the author's knowledge no normal range for platelet calmodulin has been established.

For patients who underwent brace treatment ($n=17$) or spinal fusion ($n=10$), shortly after initial evaluation calmodulin levels dropped after the institution of treatment in 82% of brace patients and 90% of those undergoing surgery. There was also a trend to higher calmodulin levels in curves greater than 30° and in patients with double structural curves although these values did not reach statistical significance. No gender difference was noted. None of the patients has been followed to skeletal maturity to see what happens to calmodulin levels in patients with progressive and non-progressive curves. Only the early results of an on-going study are summarized in this paper and we now have over 100 patients with AIS enrolled, many with only initial evaluation. The numbers at this point are too small to come to any significant conclusions about the role of calmodulin in AIS curve progression and severity.

General statements

Comment # 1

One of Dr Lowe's observations that is the most intriguing is the considerable drop in platelet calmodulin level after initiating of brace treatment or spinal fusion. I interpret this as meaning that stabilization of the deformed spine may be relieving stresses that have a negative influence on the muscle protein contractile system. This, coupled with his observation that the calmodulin level increase does not occur in patients with non-progressive curves, suggest that these curves are not overloading the muscle protein contractile system. I realize this is all very mechanistic reasoning.

Comment # 2

We had a flurry of interest in platelets in AIS and contributed to the 7th Zorab Scoliosis Symposium in 1983 [20]. In short, a platelet aggregation defect was observed

in progressive AIS but we were unable to link this with platelet glycosaminoglycans (GAGs). At that time we were much interested in GAG metabolism in AIS. Any hypothesis linking calmodulin and curve progression is on somewhat shaky ground when, as Dr Lowe has noted, "...no normal range for platelet calmodulin has been established."

Comment # 3

Dr Lowe's line of argument would make AIS a variation on neuromuscular scoliosis. Yet AIS does not resemble neuromuscular scoliosis and the patients have no neuromuscular deficit to account, in conventional theory, for their scoliosis.

Comment # 4

- a. Calmodulin seems to be ubiquitous in the biosphere, to have been remarkably conserved through evolution, to be stable and to show very little inter-species variation. There are no reports of pathology or disease process associated with calmodulin.
- b. No data are presented on normal levels of calmodulin in any species least of all humans, on possible changes in level throughout life, with growth or maturation, in sickness or in health, in times of stress or peace, between male and female.
- c. A finding of differing levels of platelet calmodulin between normal girls and those with progressive and stable scoliosis cannot be interpreted without this basic information. For example, it is conceivable, given the involvement of calmodulin in so many intracellular processes, that levels would vary with physical maturity and growth rate. In that case, adolescent idiopathic scoliosis, which is known to be locked into growth, would progress and stabilize in parallel with calmodulin levels but without any causal association.
- d. If this were true, then monitoring calmodulin levels would only give information about development, i.e. what has happened in the immediate past, since the previous visit. This information can be acquired less invasively by clinical examination and height measurement.
- e. It is suggested that adolescent idiopathic scoliosis is a "systemic disease". This is manifestly absurd. We should all remember the legal tag: *res ipsa loquitur*. The thing – the health and normality at all levels of adolescents with idiopathic scoliosis – speaks for itself. They are not diseased. They are normal healthy adolescents doing what adolescents do.
- f. I regret having to criticise a study that has involved so many people, so much good will on the part of patients, clinicians and others, but it cannot answer our ques

tions. The basic science on calmodulin should have been done first. Until then, any value in the findings will be lost in a sea of ignorance.

Response

Calmodulin is definitely ubiquitous as a calcium receptor protein. It is found in all organisms above the level of bacteria and in every type of cell in these organisms. It is similar to troponin which is found in cardiac and skeletal muscle. Calmodulin is the “troponin-like” protein found in other tissues. There have never been any diseases related to calmodulin deficiency because it is present in all tissues in large quantities, i.e. far more than is needed. This makes determining “normal levels” very difficult. Idiopathic scoliosis is not a “disease” but rather an abnormality of growth of a portion of the spine. Much of the basic science on calmodulin transmits calcium message to receptor enzymes and also modulates the intracellular ionic concentration of calcium. Calmodulin turns on the “pump” that rids the cell of unneeded calcium.

Curve severity

Comment #5

Dr Lowe states that, “There was ... a trend of higher calmodulin levels in curves greater than 30° and in patients with double structural curves although these values did not reach statistical significance”.

Question

What does Dr Lowe mean by “a trend of higher calmodulin levels ...”? There is no such thing in statistics as “a trend”.

Answer

What was meant was that there was a strong tendency for that particular relationship to approach statistical significance but that it was not actually statistically significant.

Changes in spinal deformity

Comment #6

Dr Lowe’s original observations show that *changes* in the spinal deformity of AIS are associated with percentage changes in platelet calmodulin. The change in spinal deformity may be a spontaneous progression or a decrease

brought about by surgery or brace treatment. Confirmation of these important findings is needed by other workers.

Progressive curves

Comment #7

Question

It would be helpful if Dr Lowe could elaborate quantitatively on the Kindsfater et al. [10] findings concerning platelet calmodulin levels in progressive curves.

Answer

The study by Kindsfater et al. [10] was based on a single calmodulin level in a small number of patients (17 AIS, 10 controls) and in that study we found that platelet calmodulin levels drawn on AIS patients with progressive curves were 3–4 times higher than patients with non-progressive curves or controls. The patients with non-progressive curves had similar calmodulin levels to the controls. That has not held up in the longitudinal study. In the longitudinal study only the increases in calmodulin over time in patients with progressive curves have been statistically different than the non-progressive curves and controls. The absolute values have not.

Comment #8

The EFG is very informative associating morphological and functional abnormalities of platelets with the degree and the progression of the curve in AIS in particular and possibly to all forms of scoliosis in general.

Response

The relationship of platelet calmodulin with curve progression in AIS appears to be positive and as you have noted may be positive in other types of scoliosis as well. The relationship may be related to curve progression of any etiology and not just AIS curve progression. This needs further investigation.

Effects of treatment

Comment #9

Dr Lowe reports that “calmodulin levels dropped after the institution of treatment in 82% of brace patients and in 90% of those undergoing surgery”. This implies that gross

physical manoeuvres are able to reach in and fiddle with molecular reactions. There may be simpler explanations, e.g. a secondary effect due to the reduction in mobility and normal muscle activity caused by these procedures.

Question

How can treatment (non-surgical and surgical) influence calmodulin levels? Any hypothesis?

Answer

I have pondered this question myself and have no good explanation. I guess the only thing surgery and bracing have in common is curve stabilization. Perhaps that's the reason.

Other types of idiopathic scoliosis

Comment # 10

The reported preliminary results raise interesting questions in need of answers.

Questions

- a. Are the observed morphological and functional abnormalities of platelets:
 - (i) Specific for AIS, or
 - (ii) Are they also present in other forms of scoliosis with known etiology?
- b. Have patients with IIS and JIS been compared with those with AIS?

Answers

- a) (i–ii) The only thing that we can say about the relationship between calmodulin is that it *appears* to correlate positively with *curve progression* in AIS. It may very well correlate with curve progression in scoliosis of other known or unknown etiologies. That is a question that needs to be answered after we are certain that calmodulin is a marker for curve progression in AIS and I don't think that we are that far with it yet. We need more patients with long-term data.
- b) Again, calmodulin levels have only been looked at in AIS, not in IIS or JIS. That certainly would be a worthwhile study but would require very long follow-up.

Other spinal disorders

Comment # 11

Question

Have there been any attempts to correlate platelet calmodulin with other skeletal deformities (Scheuermann's hyperkyphosis, Friedreich's ataxia etc)?

Answer

To my knowledge there have not been any attempts to correlate platelet calmodulin with other musculoskeletal conditions. I think it would be a great idea and if I can make some sense out of AIS I may do that. Perhaps we can collaborate! Unfortunately, there is a financial issue.

Muscle function, platelet calmodulin changes and AIS causation

Comment # 12

Muscle calcium metabolism and contractility in IS are considered to be associated with curve severity and progression.

Questions

Does this imply that the platelet calmodulin changes are:

- a. Acquired and related to pathomechanism(s), or
- b. Related to the etiopathogenesis of the deformity?

Answers

- a. It appears that increases in platelet calmodulin are acquired and parallel to curve progression and possibly curve severity
- b. I don't feel that changes in platelet calmodulin have any significant role in the etiology of AIS. We hope to enroll some patients with scoliosis of different etiologies to follow platelet calmodulin levels to see if they parallel AIS patients. It may very well be that increasing calmodulin levels merely reflect changes in cellular calcium and sarcomere metabolism related to changes in muscle contractility with curve progression.

Hypothesis – muscles

Comment # 13

Muscle hypothesis. Dr Lowe considers that the platelet is a “mini” skeletal muscle with a similar protein contractile system (actin and myosin) and suggests that “platelet calmodulin acts as a systemic mediator for tissues with a contractile system (actin and myosin).” [14].

Questions

- a. Can Dr Lowe speculate on possible mechanisms whereby altered platelet calmodulin levels, or consequential differences in skeletal muscle metabolism might impact at the macroscopic level on spinal and trunk function? How these might translate into abnormal morphology (scoliosis)?
- b. If skeletal muscle contraction is a factor causing increased platelet calmodulin then in cerebral palsy (with or without scoliosis) there should be increased platelet calmodulin levels. Contrariwise, in old anterior poliomyelitis (with or without scoliosis) there should be decreased levels of platelet calmodulin. Are any data available to answer these questions?

Answers

- a. We know that there are muscle abnormalities in patients with AIS both in platelets and in skeletal muscle. The consensus is that the differences in paraspinal muscle between the concavity and convexity are secondary to the deformity. Why then do platelets tend to have changes similar to convex paraspinal muscle in AIS patients? There appears to be a defective cell membrane which could be explained as atrophic changes in muscle, but why in the platelet? To me it suggests a systemic defect.
- b. To my knowledge there are no data either for platelet abnormalities or platelet calmodulin. It should be looked at.

Hypothesis – nervous system

Comment # 14

Dr Lowe does not mention the possibility that the platelet calmodulin changes may be related to a nervous system disorder – because platelets are used as a peripheral model of the nerve terminal for certain psychiatric disorders [8, 11].

Question

Could Dr Lowe please comment on this nervous system hypothesis?

Answer

I am unable to comment on the relationship of platelet calmodulin to a nervous system disorder. Certainly patients with AIS haven't been found to have an abnormality of the nervous system although with MRI I think that will be studied extensively in the near future.

Hypothesis – skeletal

Comment # 15

A skeletal hypothesis has been presented [2] to account for Dr Lowe's findings [14]. The hypothesis involves the deforming immature vertebrae of early AIS activating platelets that release growth factors from α -granules that alter the hormone-driven growth of the already mechanically-compromised disc growth plates to induce anterior spinal overgrowth and curve progression.

Question

Could Dr Lowe please comment on this platelet/skeletal hypothesis?

Answer

That certainly raises some interesting concepts that I didn't think about. I've only thought about the relationships to muscle and not bone growth. I think that the effect of large numbers of defective platelets pooling in growing osseous tissue secreting growth factors deserves some study.

Comment # 16

In a recent paper [3] it was reported “Using Lowe's data we found that percentage platelet calmodulin change correlates significantly with percentage Cobb angle change (ANOVA, $p=0.0003$, $n=54$) that led us to suggest a platelet/skeletal hypothesis to account for their findings as part of a cascade concept for the pathogenesis of AIS.” In the analysis patient no. 53 was excluded because of the 10582% increase in platelet calmodulin between the 1st and 2nd draws.

An outline of the platelet/skeletal hypothesis is published in a letter to Spine [4].

Response

I read Dr. Burwell and Dangerfield's article with great interest and would recommend that everyone following this EFG read the article in Spine [4].

Normal levels of platelet calmodulin

Comment # 17

Interestingly, a large variability in baseline levels of platelet calmodulin was noted. Clearly, this will complicate efforts to interpret the calmodulin findings both statistically and mechanistically. As noted, these observations stress the importance of obtaining baseline data from unaffected individuals.

Question

Does Dr Lowe have plans to evaluate normal platelet calmodulin levels in relation to age, differences between the sexes, puberty, the menstrual cycle, somatotype, diurnal variation, diet and exercise?

Answer

I think you have a very good point. Perhaps if we looked at male and female normal controls we could come up with some "normal" values as opposed to using patients as their own controls. We didn't have the funding to do that type of study.

Comment # 18

There are huge variations in platelet calmodulin levels that make me suspicious of their meaning. I am also uncertain about the significance/meaning of different levels in platelets from different people. It is not usually used as a marker of platelet activation.

Response

There definitely are huge variations in platelet calmodulin levels from person to person so that there is not a known normal range. This obviously complicates the study and is the reason why we didn't use age and sex-matched controls. We used each patient as their own control and only looked at changes in calmodulin levels for each patient. Absolute levels cannot be used as a marker of platelet activation. Perhaps in time, changes in calmodulin levels may provide useful information on curve progression and

stabilization by completion of growth, brace treatment, etc.

Platelets and calcium

Comment # 19

The magnitudes of the Ca and P levels, and other differences in platelet sizes, forms and behaviors noted by Yarom and co-workers [16, 17, 22, 23, 24] are not stated quantitatively in the review. These data would be helpful to assess the potential importance of the findings.

Response

I have no further data regarding Yarom's work, only what is published.

Comment and question # 20

Does Dr Lowe have any data for the calcium intake of the patients in his study?

Answer

I have no data regarding calcium intake of patients in the study.

Platelets, gender and genetics

Comment # 21

The predilection for females to develop progressive curves in AIS raises the question of whether or not there are platelet calmodulin differences between boys and girls. In platelets from female subjects the number of alpha 2-adrenergic receptors undergoes a cyclic variation that coincides with the menstrual cycle. In males no such cyclic changes were found [9]. There is recent evidence that platelet counts are higher in women than in men [1, 15].

Comment # 22

Genetics of platelet disorders. Much is known about hereditary platelet disorders that are classified according to the major locus of the defect [5].

Questions

- Are there any other gender-associated differences in relation to platelets and platelet activation?
- What is known about the effects of sex hormones and other hormones on platelet calmodulin levels?
- What is known about the genetics of calmodulin?

Answers

- All I know about platelet differences between males and females is exactly what you mentioned, i.e. the cyclic variation with menstruation and larger numbers in females. No differences in shape, size, or surface changes have been noted.
- To my knowledge there have been no effects of sex hormones on platelet calmodulin described.
- Likewise, there have not been any genetic relationships with calmodulin described that I am aware of.

Family studies of platelet calmodulin levels

Comment #23

Several hematologic – including thrombocyte disorders – aggregate within certain families.

Questions

Have:

- Siblings with AIS similar platelet anomalies, and
- Members of the family without scoliosis been examined?

Answers

- We have not looked at siblings with AIS to see if they had similar platelet anomalies but when we find siblings with AIS we will definitely look at calmodulin levels. I've thought about that a lot.*

- Our institutional review board will not allow us to look at platelet calmodulin levels in normal siblings but we have a number of adolescents with non-progressive curves and their calmodulin levels have not been found to progressively increase over time.

Melatonin and calmodulin

Comment #24

Dr Lowe states that melatonin may act by modulating calcium-activated calmodulin [13].

Question

Did Dr Lowe collect any data on melatonin in his study of platelet calmodulin?

Answer

We did not collect any data on melatonin. Dubousset and Machida [6] have looked at melatonin in AIS patients with progressive curves and noted greatly decreased levels in a group of 30 patients. There appears to be an inverse relationship but that needs to be further evaluated. Melatonin levels are very difficult to do because they must be drawn in dark rooms at night when levels are highest.

Dr Lowe's final response

I really appreciate all of the comments on this EFG. I had no idea that there would be so much interest and expertise on the subject. We still have a large number of patients in the study whose data haven't been completed. Hopefully, there will be a standardized calmodulin kit soon so that collaborative studies can be done.

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