



Fetal sensitivity to testosterone, left-handedness and development of bronchial asthma: a new approach

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Summary In contrast to Geschwind, Behan and Galaburda (GBG) theory, there is strong evidence that inheritance through maternal line is responsible for the coexistence of asthma and left-handedness early in childhood. A new model that incorporates GBG's theory and maternal inheritance is proposed. This hypothesis suggests that maternal atopy is the most important factor in the evolution of asthma and that GBG's theory applies mainly in childhood. An inherited enhanced sensitivity of fetus to testosterone may be the underlying mechanism that leads to the development of bronchial asthma.

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Central nervous system can regulate the immune system [14]. It has also been postulated that there is an association between left-handedness and allergic diseases. The Geschwind–Behan–Galaburda (GBG) hypothesis suggests that high levels of testosterone during fetal life could result to the development of left-handedness by delaying the growth of the left hemisphere. Additionally, testosterone could also affect the development of thymus, favouring the appearance of immune disorders and allergic diseases early in life [9,10].

Based on GBG's theory, the association between asthma and left-handedness has also been investi-

gated. Most researchers agree that asthma and left-handedness are related to each other in childhood and there is evidence that GBG's theory applies in asthma and allergic diseases as well [3,5,16–18]. However, there are some interesting points in this issue. In some cases, the differences observed in the distribution of Laterality Quotient (LQ) between asthmatics and non-asthmatics do not reach the level of statistical significance, especially in early childhood [1,2,16]. In our recent perspective study, asthma attacks were found to be associated with maternal anxiety and children left-handedness [12]. On the other hand, in studies of subjects after adolescence there was found no association between left-handedness and asthma [4,6]. Besides that, maternal handedness is significantly related to female offspring handedness and to the incidence

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of asthma in both males and females [8]. The inheritance of asthma does not follow Mendelian pattern of single gene disorders [7]. Recent studies revealed that maternal history of asthma or other atopic disease is a predictor of childhood asthma and left-handedness may follow the same pattern early in life [2,11,13]. If the coexistence of asthma and left-handedness early in life is mainly based on maternal line inheritance, this phenomenon could hardly be explained by the GBG's hypothesis alone.

According to Smith [16], it is not the predisposition to allergic disease itself, which is inherited, as has been assumed in the past, but rather the exaggerated testosterone levels, in utero, or the enhanced fetal sensitivity to testosterone, that runs in families and is expressed as allergic disease and left-handedness after birth. Smith also mentioned two types of sinistrality depending upon whether a familial history of left-handedness is present or not. There is some experimental evidence, which support this hypothesis [14,15]. It could also be that brain is directly involved in this process, since in rodents, lesions of right or left neocortex induced opposite effects on various immune parameters including mitogen-induced lymph proliferation, interleukin-2 production, macrophage activation or natural killer cell activity [14].

We suggest a new model that incorporates the controversial findings mentioned above. Firstly, we propose that, in accordance with Smith, it is not the predisposition to asthma and/or left-handedness itself that is inherited, but rather the enhanced fetal sensitivity to testosterone or to some other factors *in utero* which run in families and which is expressed as left-handedness or asthma after birth. The extent of this expression varies and environmental factors could modify this phenomenon. Inheritance through maternal line is suggested. In the case of maternal atopy, a most stressed hypersensitivity to testosterone that results in a permanent shift in the immune response is proposed.

On the other hand, increased levels of testosterone, or some other factors levels during fetal life lead to left-handedness through delay in the development of left hemisphere, according to GBG's theory. Thymus is also affected and allergic disorders may occur. This fact, together with environmental factors, lead to increased incidence of asthma in childhood. In this case, testosterone influence on the immune system may be less strong and the results on the immune system may be reversible. Hyperactivity of the immune system during childhood contributes to asthma manifestations. After puberty, asthma symptoms attenuate.

Two types of sinistrality are present in asthmatic children: that in which a familial history of left-

handedness can be traced and that in which no such familial history can be traced. In the first case, the fetal sensitivity to testosterone seems to be inherited. In the second one, the increased levels of testosterone are the cause. One way or another, testosterone is responsible for left-handedness.

This hypothesis suggests that inheritance through maternal line is the most important factor in the evolution of asthma and that GBG's theory applies mainly in childhood. An enhanced sensitivity of fetus to testosterone may be the underlying mechanism in both cases. The following are the new points made by this hypothesis:

1. enhanced sensitivity to testosterone is inherited through maternal line,
2. not only maternal atopy but also left-handedness is responsible for the enhanced sensitivity to testosterone through maternal line inheritance,
3. maternal atopy causes a permanent shift in the immune reaction that ends up to a long-lasting disease. Symptoms persist in adulthood,
4. testosterone consequences to the immune system might be reversible. Symptoms attenuate after adolescence,
5. two factors are responsible for left-handedness in asthmatic children. The first is the enhanced fetal sensitivity to testosterone, which is inherited through maternal line. The second is testosterone itself according to GBG's theory.

A consequence of this hypothesis is that few left-handed asthmatics are expected to be found among adults. A left-handed asthmatic child is expected to turn into a healthy adult, despite the fact that left-handed asthmatics may experience more asthma attacks in childhood than right-handed ones. The opposite happens in asthmatic children with an atopic mother. On the other hand, new data regarding asthma evolution may be emerged, if genes responsible for fetus sensitivity to testosterone are investigated.

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