Abnormal Central Complex Is a Marker of Severity in the Presence of Partial Ciliary Defect

Aline Tamalet, MD*; Annick Clement, MD*; Francoise Roudot-Thoraval, MD†; Pascale Desmarquest, MD*; Gilles Roger, MD*; Michèle Boulé, MD*; Marie Claude Millepied, TA§; Armelle Baculard, MD*; and Estelle Escudier, MD||

ABSTRACT. Background. Ciliary ultrastructural defects with total lack of dynein arms (DA) cause abnormal mucociliary function leading to the chronic infections observed in primary ciliary dyskinesia. The role of partial ciliary ultrastructural defects, especially those involving the central complex, and their relationship with respiratory symptoms have been less thoroughly investigated.

Objective. In a pediatric population with partial ciliary defects, we determined the relationship(s) between ultrastructural findings, ciliary motility, and clinical and functional features, and evaluated the outcome of this population.

Design. We analyzed the clinical presentation and pulmonary function of 43 children with chronic bronchitis and partial ultrastructural defects (from 15% to 90%) of their respiratory cilia demonstrated on bronchial biopsies. The study population was divided into 3 groups according to ciliary ultrastructure: the main ultrastructural defect concerned the central complex in 23 patients (CC group), peripheral microtubules in 8 patients (PMT group), and DA in 12 patients (DA group).

Results. The percentage of ciliary defects was lower in the PMT group than in the CC and DA groups. Patients in the PMT group had less severe disease with frequent normal ciliary motility. Patients in the CC group had initially a higher incidence of respiratory tract infections, extensive bronchiectasis frequently requiring surgery, and arguments in favor of a congenital origin (high proportion of sibling form). Partial absence of DA, although of congenital origin, was associated with a good prognosis. In all groups, follow-up showed that the functional prognosis remained good with appropriate treatment.

Conclusions. In children with chronic respiratory infections, presence of situs inversus, sibling form, obstructive pulmonary syndrome, or bronchiectasis required ultrastructural analysis, regardless of ciliary motility. Detection of CC abnormalities is a marker of severity and required intensive therapy and close follow-up. Pediatrics 2001;108(5). URL: http://www.pediatrics.org/cgi/content/full/108/5/868; respiratory tract infection, pediatric population, ciliary beat frequency, ciliary ultrastructure, bronchiectasis, pulmonary function.

ABBREVIATIONS. CBF, ciliary beat frequency; DA, dynein arms; PCD, primary ciliary dyskinesia; CT, computed tomography; FRC, functional residual capacity; FEV1, forced expiratory volume; CC, central complex; PMT, peripheral microtubules.

Airways are lined by respiratory epithelium composed of 2 main cell types, ciliated and goblet cells, which together ensure efficient mucociliary transport.1,2 Mucociliary transport is an important defense mechanism, and ciliary beat frequency (CBF) is a major parameter in airway clearance. Each cilium beats in a coordinated fashion with its neighbors, producing unidirectional mucus flow. The structural components of the core of the cilium, known as the axoneme, is highly conserved and include 9 peripheral doublet microtubules with attached dynein and radial spokes, and 2 central single microtubules (Fig 1A). Inner and outer dynein arms (DA) are the transducers of mechanical force necessary for ciliary motion. Failure of ciliary arm structure and function impairs airway clearance and can be responsible for respiratory tract infections.3–5 Ciliary insufficiency can be caused by either an inborn error or damage inflicted on the cilia by a noxious agent.6–10 Congenital defects of ciliary ultrastructure and function correspond to primary ciliary dyskinesia (PCD), including Kartagener’s syndrome, which predisposes to upper and lower respiratory tract infections beginning in early childhood.6,11,12 In the presence of a suggestive clinical presentation (eg, situs inversus, bronchiectasis, nasal polyposis), a 2-step protocol with CBF study followed by ultrastructural evaluation is classically proposed to confirm ciliary abnormalities. Although the diagnosis of PCD is easy to confirm when ciliary motility is abnormal and when all cilia share the same ultrastructural defect (eg, absence of DA), it is sometimes difficult to conclude when the ultrastructural defects do not affect all cilia and when CBF seems to be normal. However, early diagnosis of PCD with adequate prevention and therapy of respiratory tract infections may play an important role in minimizing lung damage.

In the present study, we wanted to define, in a pediatric population with partial ciliary defects, the
relationships between ultrastructural findings, ciliary motility, and clinical and functional features. We also evaluated the clinical and functional outcome of this specific population.

PATIENTS AND METHODS

Patients
Since 1985, it has been our policy to include examination of ciliary structure and function when investigating children with chronic respiratory tract bronchitis of unknown cause. Examination of ciliary structure and function was performed, in combination with other investigations, in children with chronic or recurrent lower respiratory tract infections, who were seen in the pediatric pneumology department of our institution. All these children were investigated because of the increased incidence and severity of their respiratory tract infections, occurring more than once a month for at least 6 consecutive months. Respiratory tract infections were defined by a persistent cough with bronchial ronchi, associated with or without fever. All investigations were performed in the absence of acute respiratory tract infection. Patients and their parents were informed of the exact nature and the goal any of the investigations performed and gave their informed consent. All known pathologic conditions, such as cystic fibrosis, α1-antitrypsin deficiency or immunodeficiency, were previously excluded in these children. The only abnormalities detected in some patients of our study population were partial ciliary defects.

Between 1989 and 1999, partial ciliary defects (from 15% to 95% of abnormal cilia with various axonemal defects) possibly associated with alterations of ciliary motility were detected in 50 children. Complete records for 43 of 50 patients were available for analysis in this population and these 43 children (24 boys, 19 girls, aged between 1–13 years, mean: 5.8 ± 3.3 years) constituted our study population.

Initial Evaluation
Family history of PCD (confirmed by ultrastructural analysis) and parental consanguinity were recorded. Patient history was reviewed for neonatal respiratory distress, age of onset of respiratory tract infections, and frequency of infections, classified as less than or more than 6 infections per year since birth. The number of infections was reported by parents and controlled by objective data corresponding to the pediatrician visits noted on the child’s health book. The radiologic features were studied on chest
radiograph and computed tomography (CT) scan in all cases. Situs in ver sus was noted on chest radiograph. The presence of bronchiectasis (internal diameter of bronchus larger than that of an adjacent artery) was assessed on CT scan, and its topography was scored as absent, unilateral, or bilateral. Blood gases on arterialized capillary blood were determined in all patients. Two pul monary function tests were studied in children under 7 years old: functional residual capacity (FRC) assessed by the helium dilution method and lung dynamic compliance assessed by the esophageal catheter method. After the age of 7, FRC study was combined with spirometry for determination of vital capacity and forced expiratory volume (FEV1). Results were expressed as a percentage of the expected value for age and considered as normal when >80% of the expected value.

Follow-up

The follow-up data were collected during each consultation, scheduled every 3 months. The follow-up of our patients ranged from 1 to 7 years (median: 4 years) except for 2 children who were lost for follow-up.

We evaluated and scored the frequency of antibiotic use prescribed over the entire follow-up period for their lower or upper respiratory tract infections (no antibiotics, intermittent or continuous). The course of bronchiectasis was evaluated by CT scan performed every 2 years in 25 of 41 patients and classified as stable or progressive. Radiologic deterioration corresponded to bronchiectasis extension. Pulmonary function tests were performed at least twice in 35 of 41 children, at a mean interval of 6 years. Any thoracic surgery was noted (absence of surgery or lobectomy).

Ciliary Ultrastructure and Function

Bronchial biopsies were obtained with flexible forceps introduced through the biopsy channel (Olympus Ldt, Japan, BF type 3C30 or P20D, depending on age) during fiber-optic bronchoscopy. Two bronchial mucosa specimens were sampled from the first bronchial divisions, in the absence of acute respiratory tract infection: 1 by biopsy for ultrastructural evaluation, 1 by brushing for CBF evaluation. Bronchial biopsies were immersed in 2.5% glutaraldehyde in 0.045 M cacodylate buffer at pH 7.4 and processed as usual for ultrastuctural analysis. After fixation, samples for transmission electron microscopy were postfixed in OsO4 and routinely processed. Ultrathin sections were studied at a final magnification of 60 000. At least 50 transverse sections through the body of ciliary shafts of different cells were analyzed in each specimen to study the internal axonemal structure according to a quantitative method. Ciliary arm proteins were considered to be absent from sections when the structure was missing from at least 6 of the 9 peripheral doublets. To facilitate the definition of axonemal abnormalities, the central structures (central microtubules and central sheath) were termed the “central complex” (CC). Abnormalities of peripheral microtubules (PMT) included absence of doublet(s) and supernumerary microtubule(s). Ciliary ultrastructural results were expressed as a percentage of abnormal cilia among the total number of cilia analyzed. As some cilia in control specimens can exhibit ultrastructural defects, a cut off value of 15% abnormal cilia is usually considered to be abnormal. For each ciliary study, axonemal abnormalities (involving the CC, PMT, and dynein arm [DA]) were quantified and expressed as a percentage of each ultrastructural defect among the total number of abnormal cilia and defined the main ultrastructural defect. Ciliary orientation was systematically evaluated by comparing the position of the central pairs of adjoining cilia. Disorientation was defined as an angle greater than 25°.

For CBF evaluation, the respiratory cells obtained by brushing were suspended in Menezo’s B2 medium and the sample was examined within 3 hours under a light microscope (Näehet NS 400, Paris, France) at magnifications of x 250 and x 400. CBF was measured at room temperature using computerized microscope photometry (Leitz/Leica, Wetzlar, Germany). Briefly, the cilia were positioned to interrupt a passage of light through a small diaphragm in the Leitz MPV compact microscope photometer. This light intensity was converted into an electric signal that was subsequently expressed as CBF in Hz using a CBF processor unit. For each patient, ciliary beat frequency was determined on at least five different areas of ciliated epithelium and a mean value was calculated. When only immotile cilia were observed, CBF was considered to be 0 Hz. According to the literature, ciliary motility was considered to be normal when CBF was greater than 8 Hz, and abnormal in the case of immotile cilia or when CBF was less than 8 Hz.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD), or as percentages. For comparison of quantitative data, Mann-Whitney and Kruskal-Wallis tests were used to compare data classified in two or more categories, respectively. When necessary, the Pearson χ² test or the Fisher exact test was applied to assess the relationship between categorical data. P ≤ .05 was considered to be significant.

RESULTS

The study population was divided into 3 groups according to the ciliary ultrastructural results: the main ultrastructural defect involved the CC in 23 patients (54%), PMT in 8 patients (18%), and DA in 12 patients (28%; Fig 1).

The results of ciliary studies and the various clinical, radiologic, and functional parameters established at the initial assessment and during follow-up were then evaluated and compared between the 3 groups.

Analysis of Ciliary Ultrastructure and Relationship With Ciliary Motility

The mean percentages of ciliary abnormalities were statistically different (P < .03) between the CC, PMT, and DA groups (39.4 ± 18.7%, 28.4 ± 15.7%, 56 ± 28%, respectively; Fig 2). The mean percentages of the main ultrastructural defect were similar in the CC, PMT, and DA groups (79.7 ± 19.6%, 70 ± 15.6%, 82.6 ± 18.9%, respectively). Although the difference was not statistically significant, the percentages of patients with abnormal ciliary motility were higher in the CC and DA groups, 75% and 83%, respectively compared with 25% in the PMT group (Fig 3, Table 1). It should be stressed that no patient in the PMT group had immotile cilia and that ciliary motility was never normal when the ultrastructural defects affected >60% of the cilia. Ultrastructural abnormalities and ciliary orientation were not related to each other (data not shown).

Fig 2. Results of ciliary ultrastructure according to the main ultrastructural defect. Horizontal lines indicate the mean.
Clinical and Functional Evaluation in the 3 Groups

Comparison of the various parameters of the initial and follow-up assessments between the 3 subgroups is shown in Table 1. Mean age at diagnosis was 5.8 ± 3.3 years and was similar in the CC, PMT, and DA groups (6.7 ± 3.5 years, 5.4 ± 3 years, 5.3 ± 4 years, respectively). The incidence of neonatal respiratory distress and the age of onset was similar in the three groups. Situs in versus was only observed in the DA group (6/6), and all but 1 of the sibling forms belonged to the CC group (8/9). The incidence of consanguinity was similar in the 3 groups. Patients in the CC group had more frequent lower respiratory tract infections (56.5%) than patients in the PMT or DA groups (25% and 16.7%, respectively; P < .05). A similar difference was observed for bronchiectasis: 69.6% vs 57% and 50% in the MTP and DA groups, but was not significant. It must be noted that bronchiectasis was bilateral in 47.8% of cases in the CC group versus 14% and 30% in the other groups.

Follow-Up

Serial pulmonary function tests were performed at the ages of 6, 9, and 12 years in 33 children. Mean follow-up (about 3 years) was shorter for the PMT group. The mean arterial P<sub>0</sub> was in the normal range in each group (CC group: 81 ± 10 mm Hg, DA group: 89 ± 11 mm Hg, PMT group: 88 ± 12 mm Hg). Obstruction, evaluated for the youngest patients by dynamic lung compliance, was lower in the CC group (57.4% of predicted value) than in the DA group (69% of PV). After the age of 7 years, obstruction evaluated by FEV<sub>1</sub> was lower in the CC group (82 ± 24% of predicted value) than in the DA group (96 ± 5% of predicted value), but remained within the normal range. The results in the PMT group could not be compared with those of the other groups, as FEV<sub>1</sub> was measured in only 2 patients in this group.

Treatment included chest physiotherapy, and continuous or intermittent antibiotics for all patients studied. Antibiotic use and radiologic deterioration were similar in the 3 groups (Table 1). The incidence of thoracic surgery was significantly higher (P < .05) in the CC group (52.2%) than in the other groups (12.5% in the PMT group and 14.7% in the DA group). Pulmonary function remained stable throughout the study period. FEV<sub>1</sub> showed a similar trend and was always greater than 80% of predicted values for healthy participants (data not shown). The degree of distension, reflected by FRC, tended to increase, but remained within the normal range (initially in the CC group, in the DA group and in the PMT group, 89 ± 15%, 96 ± 15% and 101 ± 11%, of predictive values, respectively; after 6 years of follow-up in the CC group and the DA group, 99 ± 15% and 93 ± 10%, respectively). The results in the PMT group could not be compared with those of the other groups, as FRC was measured in only 2 patients in this group.

DISCUSSION

Comparison between ciliary studies and clinical presentation of patients with partial ultrastructural defects showed that the severity of the respiratory disease was related to the type of ultrastructural defect but not to ciliary motility. In our population, no strict relationship was demonstrated between the main ultrastructural defect and CBF in accordance with previous reports. Abnormal CC was associated with a higher frequency of respiratory tract infections and extensive bronchiectasis frequently requiring surgery, suggesting a more severe disease. On the other hand, in every case, follow-up showed that the functional prognosis remained good when the patients received appropriate therapy.

The percentage of ultrastructural defects was significantly lower in the PMT group than in the CC and DA groups. Compared with the other groups, the PMT group contained fewer patients. These patients seemed to have less severe disease with frequently normal ciliary motility, initially fewer infections, and a lower incidence of surgery. Abnormalities of PMT are considered to be acquired ciliary defects, usually observed in patients with chronic or recurrent infection. In the PMT group, limited zones of bronchiectasis, absence of situs inversus, and a low incidence of familial cases constitute arguments in favor of a non congenital origin of their respiratory disease. The cause of respiratory tract infections remains unknown in this group, even after ciliary studies and other etiologic investigations. The frequently normal ciliary function with low percentage of abnormal cilia strongly suggests that ciliary abnormalities are not responsible for respiratory tract infections in these patients. During follow-up, these patients required more antibiotics to control their pulmonary infections, which could be related to an unknown disease (ie, as yet unidentified minor immunodeficiency, which could be at least partially controlled by antibiotics).
TABLE 1. Clinical and Familial Characteristics in the 3 Groups Defined by the Main Ultrastructural Defect

<table>
<thead>
<tr>
<th></th>
<th>CC Group (n = 23)</th>
<th>PMT Group (n = 8)</th>
<th>DA Group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal cilia (%)</td>
<td>39.4 ± 18.7</td>
<td>28.4 ± 15.7</td>
<td>56 ± 28</td>
</tr>
<tr>
<td>Abnormal CBF (n = 29, %)</td>
<td>74</td>
<td>25</td>
<td>83</td>
</tr>
<tr>
<td>Age of onset (mo)</td>
<td>18 ± 16</td>
<td>20 ± 13</td>
<td>13 ± 11</td>
</tr>
<tr>
<td>Age of diagnosis (y)</td>
<td>6.7 ± 3.5</td>
<td>5.4 ± 3</td>
<td>5.3 ± 4</td>
</tr>
<tr>
<td>Situs inversus (n = 6)</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Consanguinity (n = 11)</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Sibling form (n = 9)</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neonatal distress (%)</td>
<td>27</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Infections† (&gt;6/y)</td>
<td>56.5</td>
<td>25</td>
<td>16.7</td>
</tr>
<tr>
<td>Bilateral bronchiectasis</td>
<td>47.8</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic use (%)</td>
<td>56.5</td>
<td>62.5</td>
<td>41.7</td>
</tr>
<tr>
<td>Radiological deterioration (%)</td>
<td>40</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Lobectomy† (%)</td>
<td>52.2</td>
<td>12.5</td>
<td>14.7</td>
</tr>
</tbody>
</table>

* Results are expressed as the percentage of patients in each group, except for situs inversus, sibling form, and consanguinity, which are expressed as the number of patients in each group.
† P < .05.
‡ Discontinue and continue use of antibiotics. Radiological deterioration corresponds to extension of bronchiectasis.

Absence of DA was the first ultrastructural defect described in PCD, and it remains the most common defect. However, some authors have reported that a partial or local DA defect could be observed in some patients with acquired bronchiectasis. Although absence of DA usually occurs as a single abnormality affecting all cilia, this specific defect has also been described as a partial defect, affecting variable percentages of cilia in PCD patients. In these cases, it has been postulated that either dynein protein synthesis or its assembly on microtubules could be partially deficient. In our study, all cases of situs inversus were associated with DA ultrastructural defects, as classically described. This is a strong argument in favor of the congenital nature of the respiratory disease affecting patients of the DA group. The different genetically determined ultrastructural defects of cilia described in patients with PCD are also reported in flagellar mutants of Chlamydomonas reinhardtii. Interestingly, some of the Chlamydomonas DA mutants (eg, pf-23 and pf-13 with partial defects of inner and outer DA, respectively) are somewhat incomplete, like the comparable mutants observed in humans. Patients in the DA group could represent sporadic cases of a congenital disease, ie, PCD with variable penetrance.

Partial CC defects were observed in 54% of the study population and were the most frequent ultrastructural defect observed. CC abnormalities are not well defined compared with the absence of DA. A consensus has not been reached concerning the significance of missing of central microtubules. This specific defect has been reported in the context of acquired and recurrent infections, but only a few cilia are affected. On the other hand, abnormalities of central microtubules are described in human spermatozoa and in Chlamydomonas mutants, confirming their constitutional nature. Central microtubule defects, mainly reported in human spermatozoa, usually affect the total sperm population. In respiratory ciliated cells, CC abnormality is mostly considered to be of congenital origin, although ciliary motility could be normal and ultrastructural defects are never detected in more than half of the cilia. An association between situs inversus and abnormal CC has not been reported in the literature, but a number of arguments are in favor of the congenital origin of abnormal CC in our study. As in another study, a high proportion of patients presented familial CC abnormalities. An important finding is that patients with CC defects had a severe clinical presentation as they tended to have a high incidence of respiratory tract infections (mainly bilateral bronchiectasis) leading to extensive bronchiectasis requiring pulmonary resection. The clinical severity observed in the CC group could not be simply explained by abnormal ciliary function, as ciliary motility abnormalities were observed equally in both the CC and DA groups. Three hypotheses could explain partial CC defects: 1) particular instability of central microtubules; 2) short central microtubules present only in the basal part of the cilia; and 3) quantitative synthesis deficiency providing central microtubule structures for only some cilia.

The last interesting aspect of this pediatric study is the encouraging follow-up data showing that lung function did not deteriorate during the observation period, lasting for 3 to 6 years. The pulmonary function of PCD children is initially normal in the majority of cases, but can deteriorate during the course of the disease. In our pediatric study, initial pulmonary function was also normal, except for dynamic lung compliance, a parameter not evaluated in previous studies. In patients younger than 7 years, this functional test demonstrated that lung obstruction was more pronounced in the CC group than in the other groups. In older children, in whom spirometry was performed, patients in the CC group still exhibited a certain degree of obstruction compared with the other patients. These findings are in agreement with the few previous reports concerning the follow-up of pulmonary function in PCD patients. Airway obstruction and air trapping with distension are frequently observed in adult PCD patients. However, in the literature, as in our study, pulmonary function stabilizes for several years with appropriate
treatment.28 Similarly, extension of bronchiectasis was observed in <30% of our patients and was not related to the type of ultrastructural defect, as already suggested.29 In fact, the slow progression of radiologic lesions seems to be exclusively related to age.30 These findings emphasize the importance of early diagnosis of ciliary dyskinesia, and propose a close follow-up, with appropriate antibiotic treatment and physiotherapy and to prevent lung damage.

CONCLUSION

In the presence of a suggestive clinical pattern, the diagnosis of ciliary dyskinesia is difficult to confirm when some cilia are normal or when all cilia do not share the same ultrastructural defect. In the present study, we defined the relationships between ultrastructural findings, ciliary function and clinical features. Significant differences were found when comparing clinical features and ultrastructural phenotype showing that the type of the main ultrastructural defect was more closely correlated with the clinical presentation than the percentage of abnormal cilia.

Analysis of the main ultrastructural defect demonstrated significant differences between patients. We identified that in children with chronic respiratory tract infections and partial ciliary defects, CC abnormalities was a marker of severity. This specific axonemal defect, already reported in PCD, never concerns more than half of the cilia, but is probably congenital. For these patients, it is first necessary to confirm the ultrastructural defect on another biopsy, preferably performed at an other level of the respiratory tract, eg, nasal biopsy. Secondly, intensive antibiotic therapy and close follow-up are especially required for these patients. Finally, it will be interesting to proceed to genetic analysis, when it will be possible. Conversely, partial absence of DA is associated with a good prognosis, but only identification of a specific genetic abnormality will be able to confirm that this specific axonemal defect represents a partial form of PCD. Finally, the origin of respiratory tract infections is not explained by ciliary studies in PCD patients in the PMT group and requires further investigation. It should be noted that some CC and DA defects won’t be detected when ciliary ultrastructural analysis is only performed in cases of abnormal ciliary beat frequency. Some clinical features, such as situs inversus, sibling form, obstructive pulmonary function parameters, and extensive bronchiectasis are more suggestive of PCD than age of onset of respiratory tract infections, neonatal respiratory distress or consanguinity. In the presence of such a suggestive clinical pattern, quantitative and qualitative ultrastructural analysis should be recommended, regardless of CBF results. Early diagnosis is particularly important, as the prognosis remains good even after lung surgery with physiotherapy and appropriate antibiotic treatment.

ACKNOWLEDGMENT

We thank Professor André Coste (Hôpital H. Mondor, Créteil) for his pertinent advice in preparation of this manuscript.
Abnormal Central Complex Is a Marker of Severity in the Presence of Partial Ciliary Defect

Aline Tamalet, Annick Clement, Francoise Roudot-Thoraval, Pascale Desmarquest, Gilles Roger, Michèle Boulé, Marie Claude Millepied, TA§; Armelle Baculard and Estelle Escudier

Pediatrics 2001;108;e86
DOI: 10.1542/peds.108.5.e86

Updated Information & Services
including high resolution figures, can be found at:
/content/108/5/e86.full.html

References
This article cites 30 articles, 4 of which can be accessed free at:
/content/108/5/e86.full.html#ref-list-1

Citations
This article has been cited by 1 HighWire-hosted articles:
/content/108/5/e86.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
/cgi/collection/infectious_diseases_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2001 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.
Abnormal Central Complex Is a Marker of Severity in the Presence of Partial Ciliary Defect
Aline Tamalet, Annick Clement, Francoise Roudot-Thoraval, Pascale Desmarquest, Gilles Roger, Michèle Boulé, Marie Claude Millepied, TA§; Armelle Baculard and Estelle Escudier

Pediatrics 2001;108;e86
DOI: 10.1542/peds.108.5.e86

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/108/5/e86.full.html