Acute flaccid paralysis by non-polio exteroviruses before, during and after eradication of poliomyelitis

Subhash C. Arya, MBBS, PhD.

ABSTRACT
Episodes of acute flaccid paralysis (AFP) by one or more coxsackieviruses, type A 4, 6, 7, 9, 11, 14, 21, type B 1 to 6, echovirus type 1 to 4, 6, 7, 9, 11, 14, 16, 18, 19 and 30 or enterovirus type 70, 71 and 72, infections have been described for many decades. Following international plans to eradicate poliomyelitis by the end of the century, non-poliovirus enteroviruses were reported to cause acute flaccid paralysis in Latin America even after a successful eradication of poliovirus-induced AFP. Recently, enterovirus 71 was incriminated for infantile AFP in Brazil with a clinical picture similar to paralytic poliomyelitis. Well-designed laboratory support is needed to ascertain the role of non-polio enteroviruses (NPEV) in episodes of AFP in various countries irrespective of the national poliomyelitis eradication or control activities. MRI examination for the central nervous system pathology with sagittal spin-echo proton density and T-2 weighted images should localize hyperintense bands corresponding to anatomic location of ventral horn and other target nuclei for NPEV lesions. An early lead towards neuronal involvement could ensure therapeutic usage of interferon-alpha to alter disease progression, with an uneventful recovery. Apart from MRI, demonstration of poliovirus or NPEV-specific IgM in saliva or CSF, by rapid, simple, assay procedures, could guide the clinicians to a prompt therapy in patients with AFP. As a prelude to control of NPEV-induced AFP in future, it would be desirable to obtain base-line data for neurovulrence in simian nervous tissues as collected with polioviruses during the 1940's. Fiscal allocation towards basic research including a specific, rapid NPEV diagnosis would be more than cost-effective.

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Acute flaccid paralysis (AFP) is the clinical expression of neuronal injury with denervation and muscular atrophy of disuse. AFP has been responsible for a remarkable mortality and morbidity for considerable period all over the globe. After availability of inactivated and attenuated poliovirus vaccines during the 1950s, there was a remarkable decrease in incidence of AFP attributable to wild polioviruses in industrialized countries. In developing countries, there was little respite and as many as 500 cases of poliomyelitis-associated AFP were reported daily in India during the 1980's. The impact of the WHO strategy of elimination of poliomyelitis towards the end of the century, was evident in Latin America during the early 1990s itself. During 1990, only 15 cases of poliovirus-induced AFP were recorded in Latin American countries as against an estimated 116,000 cases that occurred globally. The three integral components in the WHO strategy of national immunization days, mopping up operations and high quality surveillance, have failed to eliminate AFP from Latin America. During 1989, 1990, and 1991, there were 1912, 2019 and 2044 cases of AFP, with non-poliavirus enterovirus (NPEV) responsible for 56%, 69% and 75% episodes of AFP. Recently, enterovirus 71 was responsible for persistent AFP in eight geographic areas in Brazil and 20 of the 92 patients were positive for enterovirus 71 IgM. NPEV have been well documented to be associated with AFP right after the availability of sophisticated tissue cultural facilities for growth and isolation of viruses. Recently, it has been possible to localize neuronal damage attributable to attenuated poliovirus vaccine strains as well as to other non-polio enterovirus replication. The response in one child

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Table 1 - Etiological entities of acute flaccid paralysis

<table>
<thead>
<tr>
<th>Disease or syndrome</th>
<th>Salient features</th>
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<tbody>
<tr>
<td>Poliomyelitis</td>
<td>Lesions are asymmetrical caused by wild virus, vaccine virus or by emerging chimaeric or recombinants</td>
</tr>
<tr>
<td>Diplegia (cerebral palsy)</td>
<td>Associated with prematurity with cerebral infarction or hemorrhages that affect lower limbs. Extensor paralysis is evident at 6 months with strong hip adduction. Later, spastic, stiff-legged, clumsy gait is seen.</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
<td>Caused by demyelination with axonal degeneration. The paralysis is symmetrical with sensory changes and pyramidal signs.</td>
</tr>
<tr>
<td>Acute motor neuropathy or Chinese paralytic syndrome</td>
<td>A symmetrical disorder due to chromatolysis of anterior horn cells with dispersion of Nissl substance. The motor roots show demyelinating changes and Wallerian-like degeneration.</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>An interruption of motor and sensory tracts at one level, usually thoracic, leads to bilateral paraplegia and paraparesis progressing to paraplegia.</td>
</tr>
<tr>
<td>Injury to nerves, traumatic neuritis</td>
<td>After birth injuries due to traction or breech delivery or spinal nerve injury after intramuscular injection. Purely motor loss with little sensory loss and foot-drop with paralysis of muscles supplied by common peroneal nerve.</td>
</tr>
<tr>
<td>Hypokalemia in malnourished children</td>
<td>Severe manifestation of head lag with quadriplegia. Respiratory paralysis might require respiratory support.</td>
</tr>
<tr>
<td>Hopkins syndrome</td>
<td>Polio/myelitis-like illness with a flaccid paralysis of an extremity during the recovery stage of an asthmatic attack.</td>
</tr>
<tr>
<td>Non-poliovirus enterovirus - induced paralysis</td>
<td>Differntiation might be possible by serological, virological, molecular biological techniques and/or by MRI or proton magnetic resonance spectroscopy.</td>
</tr>
</tbody>
</table>

and an adult who had AFP attributable to poliovirus, to interferon-alpha therapy, was associated with a clinical improvement within a day or so. The clinician could alter progression of AFP through an early therapeutic intervention if it was feasible to establish a specific diagnosis for the etiological agent responsible for AFP in such cases. The relevant issues to be encountered for a prompt diagnosis, specific treatment and prevention of non-poliovirus enterovirus induced AFP are addressed in the present communication. Non-poliovirus enterovirus AFP would have to be prevented even in areas certified to be free of poliomyelitis.  

**Differential diagnosis of AFP.** The clinicians are obliged to differentiate between different clinical entities that have been associated with AFP (Table 1).  

Wild poliovirus strains are reported to cause AFP in industrialized countries with a good vaccine coverage. There are reports of vaccine-associated AFP among recipients or their contacts in rare instances. Seven different coxsackievirus type A, six coxsackievirus type B strains, 13 echoviruses strains and three enterovirusese are known to cause AFP (Table 2).

Apart from infection by polioviruses, non-poliovirus enteroviruses, a temporal association between the isolation of Sabin-related vaccine strains has been described for Guillain-Barre syndrome and transverse myelitis. Furthermore, apart from AFP attributable to a viral infection, clinicians encounter AFP related to trauma and metabolic alterations.  

**Guillain-Barre syndrome.** An acute demyelinating polyneuropathy with progressive, most often ascending paralysis of the body, is accompanied by symmetrical manifestations and sensory changes. Pyramidal signs are observed and the demyelination is associated with variable axonal degeneration.

**Transverse myelitis.** An interruption of motor and sensory tracts at one level, usually thoracic, leads to bilateral paraparesis, paraplegia that progress to paraplegia.  

**Diplegia.** A cerebral infarction or hemorrhage in premature births is associated with a cerebral palsy. An extensor paralysis of lower limbs is evident at 6 months of age with a strong adduction at hips. Later, the gait is spastic, stiff-legged and clumsy.

**Acute motor neuronopathy or Chinese paralytic syndrome.** This syndrome is a symmetrical disorder with a tendency towards recovery. The syndrome is not only confined to China but has been reported in Bangladesh as well. There is chromatolysis of anterior horn cells with dispersion of Nissl substance. Motor root involvement is associated with mild demyelinating changes and Wallerian-like degeneration.

**Injury to nerves including traumatic neuritis.**

Table 2 - Enteroviruses known for causation of acute flaccid paralysis

<table>
<thead>
<tr>
<th>Type</th>
<th>1, 2, 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poliovirus type</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Coxsackieviruses type A</td>
<td>4, 6, 7, 9, 11, 14, 21</td>
</tr>
<tr>
<td>Coxsackieviruses type B</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Echoviruses type</td>
<td>1, 2, 3, 4, 6, 7, 9, 11, 14, 16</td>
</tr>
<tr>
<td>Enteroviruses type</td>
<td>70, 71, 72</td>
</tr>
</tbody>
</table>
injury to sciatic nerve following an injection may be followed by nerve loss with little sensory involvement. The paralysis of the muscles supplied by the common peroneal nerve leads to foot-drop. Birth injuries associated with traction or breech delivery could as well manifest as AFP.

**Hypokalemia in malnourished children.** Severe hypokalemia in malnourished children could manifest as AFP with paralysis varying from neck flop to quadripareisis. Respiratory paralysis might require a ventilatory support. A successful treatment with potassium supplementation to tackle hypokalemia in malnourished children would ensure a rapid recovery from AFP.

**Hopkins syndrome.** During the recovery phase of an asthmatic attack, AFP could manifest with a poliomyelitis-like illness with involvement of an extremity. In a 7-year old boy with Hopkins syndrome, high intensity areas were observed in the left anterior horn at cervical cord 4 to 6 level, during T2-weighted MRI of the central nervous system.

**Miscellaneous entities.** The clinical entities often misdiagnosed as an AFP attributable to poliovirus, have included osteoarticular trauma, myopathies dystrophies, viral myositis, acute cerebellitis, retroperitoneal tumors and upper motor neurone syndromes. The clinicians would be able to diagnose episodes of AFP specifically following availability of rapid laboratory tests as well as MRI on brain and spinal cord of their patients.

**Advances towards a specific diagnosis and care of AFP.** The recent progress in laboratory technology, proton magnetic resonance spectroscopy as well as MRI should assist in a judicious patient care with AFP.

**Laboratory support.** The conventional technology of isolation of virus responsible for an episode of AFP involves cultivation of virus in cell cultures, blind passages, neutralization of cytopathic agents and in-vivo test for neurovirulence. Serological evidence of an enterovirus infection is available through demonstration of rising IgG antibody titre. The process is complicated, requires sophisticated laboratories and is time consuming. Nevertheless, μ-capture assays to measure poliovirus-specific IgM antibodies for three serotypes in serum and CSF in patients with clinically labelled acute poliomyelitis have appeared to be sensitive and specific for confirmation of a specific diagnosis of poliomyelitis.

**Proton magnetic resonance spectroscopy.** The functional activity of neurones could be monitored by demonstration of significant metabolic alterations around individual motor neurones. In a 53-year old woman with Creutzfeldt-Jakob disease, neuronal loss could be demonstrated by reduced N-acetylaspartate peak, reduced creatinine/phosphocreatine ratio and increased sorbitol.

**Magnetic resonance imaging (MRI).** The pathologic picture in neurones in the anterior horns of the spinal cord were ascertained by T-2 weighted MRI in a 7-year old boy who developed acute flaccid paralysis of the left upper limb 4 days after an asthmatic attack. High-intensity areas were observed at cervical levels 4 to 6. MRI of the cervical spine at the Rhode Island Hospital in a 27-year-old man who developed AFP three weeks after his 20 month-old infant was immunized with trivalent live poliovirus vaccine, revealed smooth hyperintense bands. Sagittal-spin proton-density weighted and T2-weighted images revealed involvement of region corresponding to anatomic location of the ventral horns. CSF cultural studies were positive for poliovirus type 3, with no isolation from stool cultures and normal antibody titers. By MRI, lesions in the dorsal region of the pons to the upper part of the thoracic cord were evident in a patient with poliomyelitis-like syndrome at Ehime in Japan. There were hypointense T1-weighted lesions with a bilateral horn involvement. The laboratory studies were inconclusive, a poliovirus-like syndrome caused by NPEV was suspected as the causative agent of AFP in the seven-month infant. The current technology of rapid diagnosis of an enteroviral infection, proton magnetic resonance spectroscopy as well as MRI should assist in selection of AFP patients most likely to respond to interferon therapy.

**Interferon therapy for AFP.** The response to interferon treatment for poliovirus-induced AFP was encouraging in two patients during the 1980s. A 16-month infant and 34-year old man with bulbar paralysis, due to wild virus type 1 and vaccine strain type 2, were offered 1 and 3 million units, respectively, or interferon-alpha, intramuscularly for 16 days. Interferon halted clinical progression within 24 hours and an improvement was evident within a day or two. Early interferon therapy could alter disease progression and alter AFP induced disability.

**Future management of episodes of AFP.** The global eradication of poliomyelitis by the beginning of the next century would not be associated with elimination of AFP attributable to other enteroviruses (Table 2). An integrated approach involving neurologists and primary care clinicians, researchers and public health personnel should minimize the residual disability attributable to infectious or non-infectious causes of AFP (Table 1).

**Early diagnosis and therapy.** Simple, 1-2 step, tests that do not require costly equipment and trained personnel would be invaluable to primary care.
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clinicians for an early diagnosis of NPEV induced AFP. Efforts should be directed to quantify NPEV specific IgM immunoglobulins in saliva rather than blood or CSF. The non-invasive, rather than invasive techniques relying on CSF examination, would be preferable in developing countries with poor budgetary allocation for sterile equipment. Both proton magnetic resonance spectroscopy and MRI would be invaluable assets for the neurologists at referral centres for a qualitative and quantitative assessment of poliovirus or NPEV-induced necrosis of target neurones in brain and spinal cord. These investigations would ensure a prompt interferon therapy with the least residual disability. Serial MRI would enable an objective follow-up to interferon-alpha therapy.

Research input. Fiscal input is desirable to ensure availability of simple laboratory test, to obtain seroepidemiological profiles of various NPEV associated with AFP (Table 2), and to ascertain neurovirulence of NPEV by in vivo tests.

Simple laboratory tests. Apart from the μ-capture test that employs S-methionine-radiolabelled poliovirus for assaying poliovirus-specific IgM, it is imperative that simple, 1-2 step assay procedures are standardized for detection of NPEV-specific IgM in saliva. Fiscal input towards standardization of such devices would be cost-effective. A prompt diagnostic lead would be followed by specific therapy and prevention.

Epidemiological profiles of NPEV. The academic and research efforts have been directed to study seroepidemiology of poliovirus infection in industrialized and developing countries in different rural and urban communities. Similar base-line data would have to be worked out with different NPEV. The basic information would reveal magnitude of NPEV infection in areas where poliomyelitis has been eradicated or was likely to eradicate in the near future.

Neurovirulence of NPEV. Basic information on neurovirulence of wild polioviruses was obtained during the 1940s, while inter-species neurovirulence of attenuated poliovirus strains was established by international collaboration during the 1970s. Similar data would be needed with different NPEV for their neurovirulence in monkeys or transgenic mice susceptible to poliovirus multiplication.

Epilogue. The eradication of poliovirus-induced AFP by the beginning of the next century would not imply eradication of AFP attributable to NPEV. Appropriate strategy would have to be coordinated at international and national level to tackle AFP by NPEV. Availability of a vaccine for NPEV would be dependent on characterization of NPEV neurovirulence and selection of relevant strains. The infrastructure for global eradication of poliomyelitis, could very well be entrusted the responsibility for obtaining basic epidemiological information on AFP induced by NPEV and to eventually design strategies for the global control of the 21st century episodes of NPEV-induced AFP globally.

References

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